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A.M.A. ARCHIVES OF OPHTHALMOLOGY

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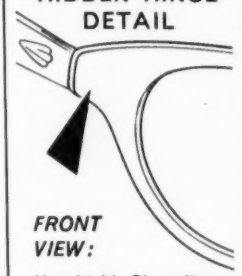

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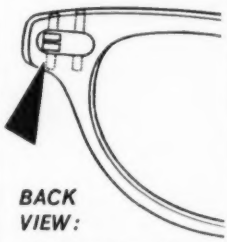

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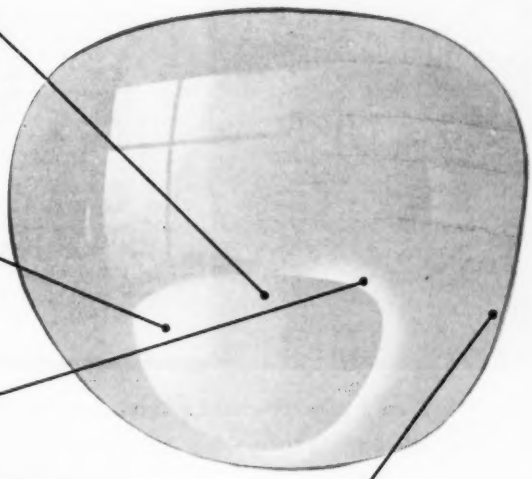

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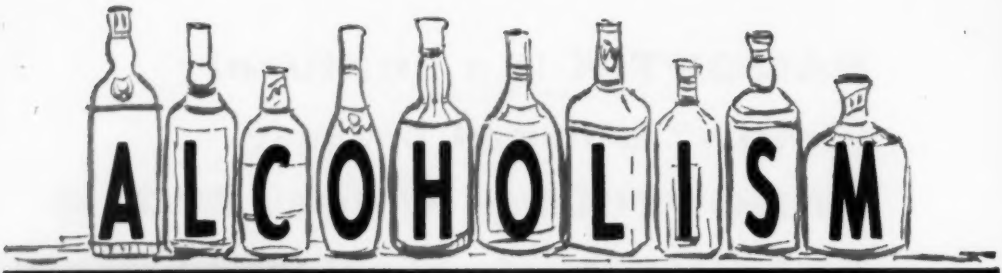

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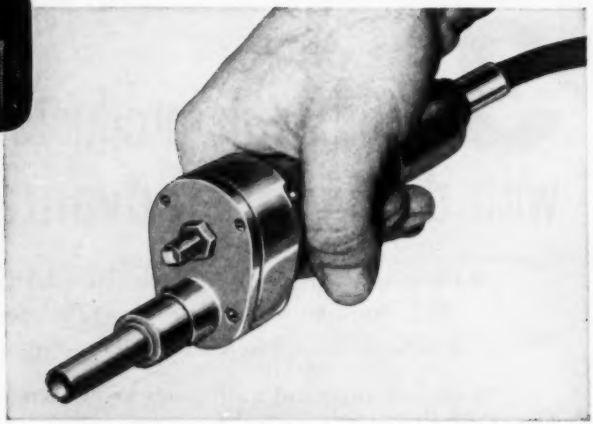

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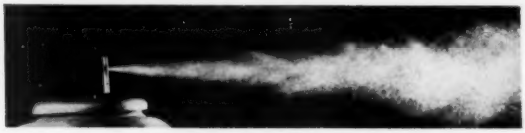

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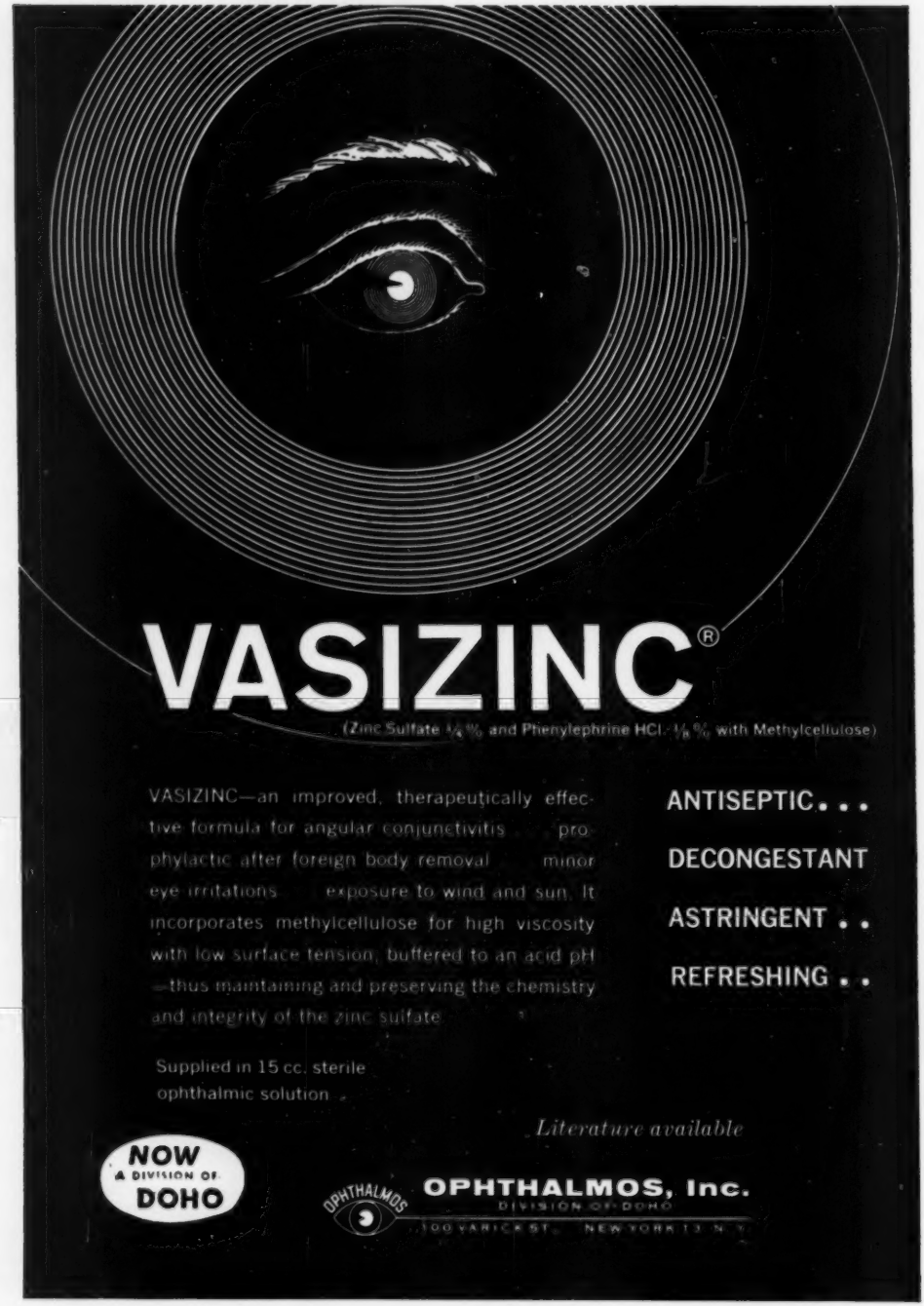
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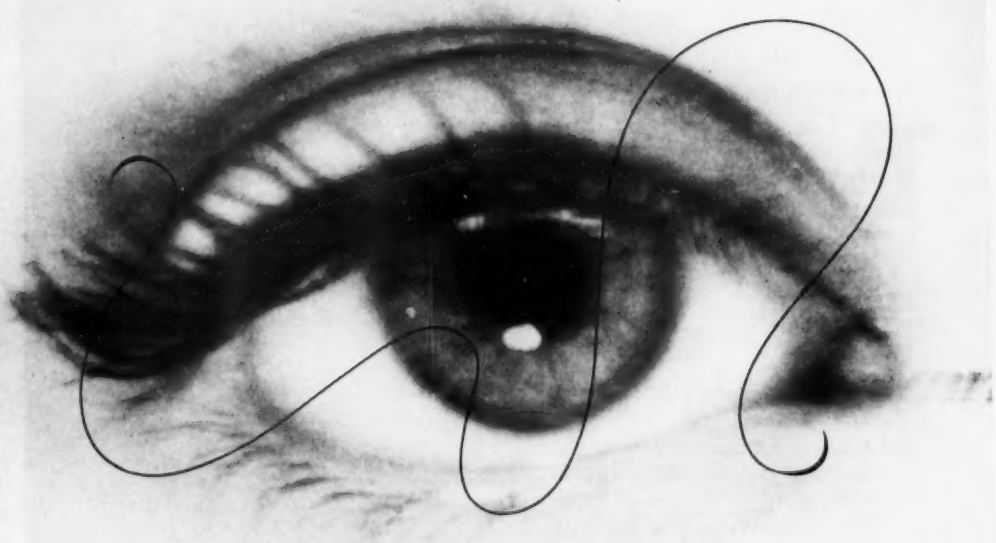

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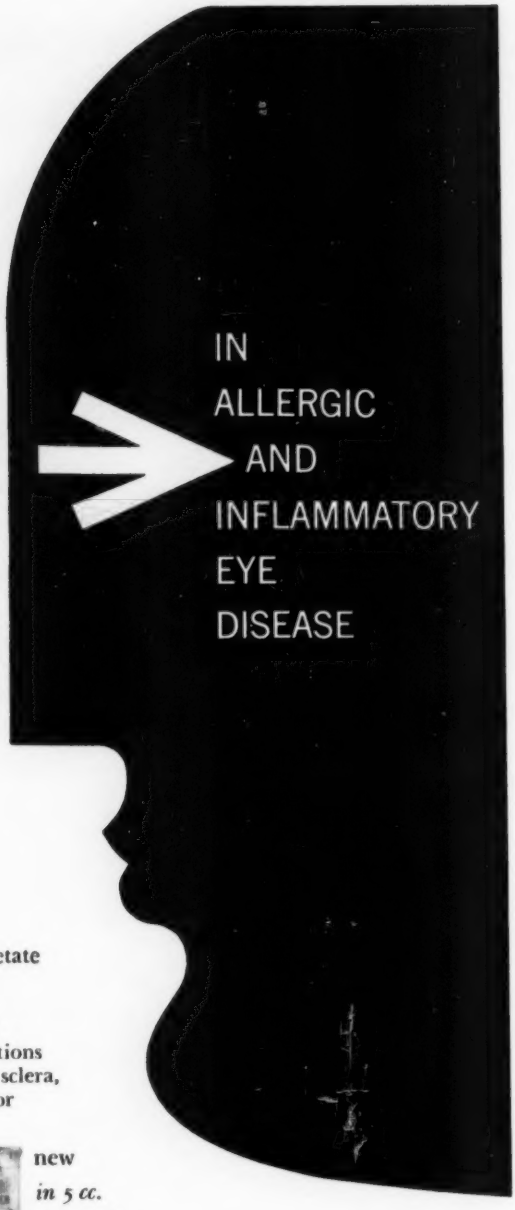

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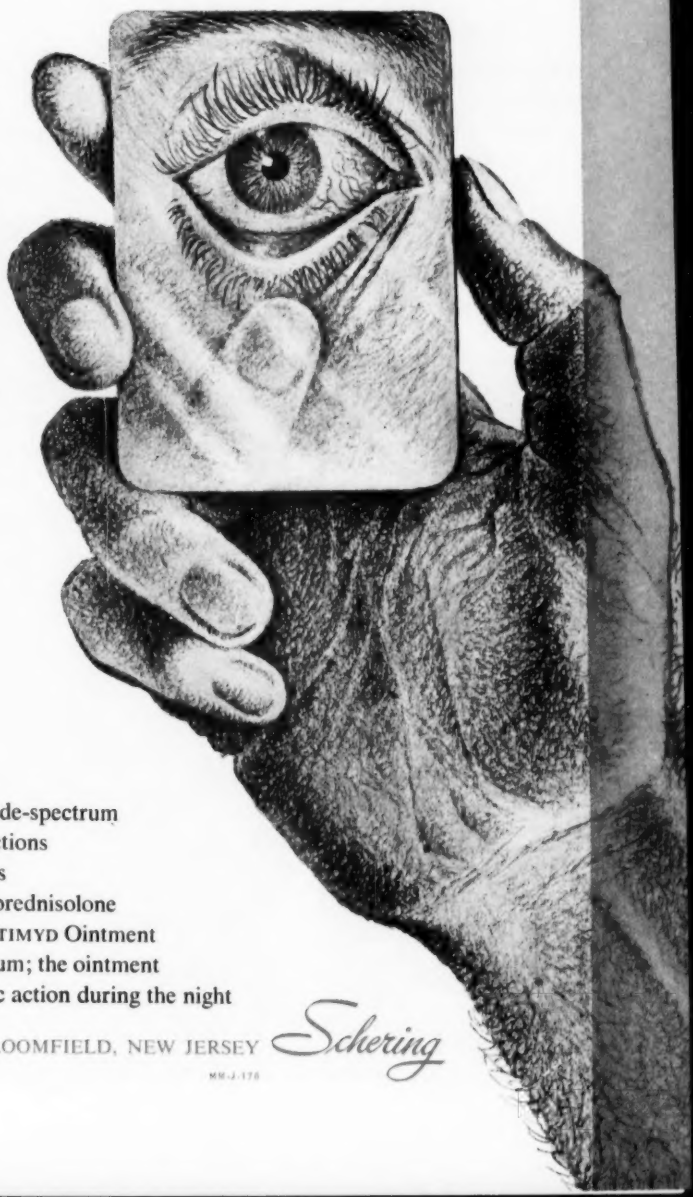

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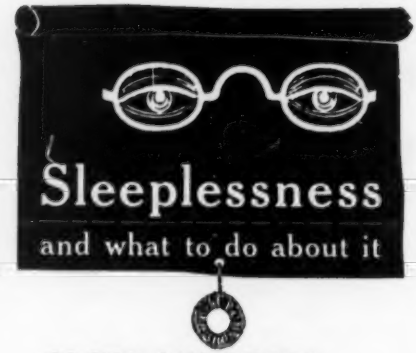

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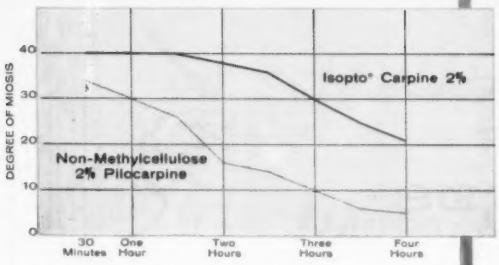

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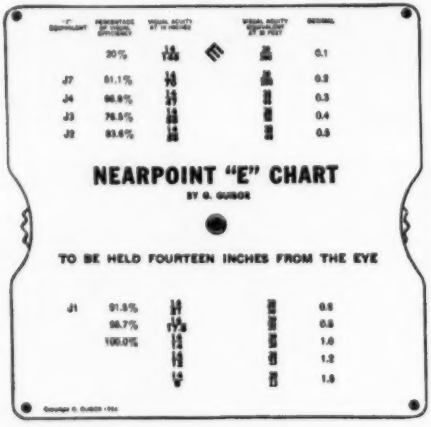

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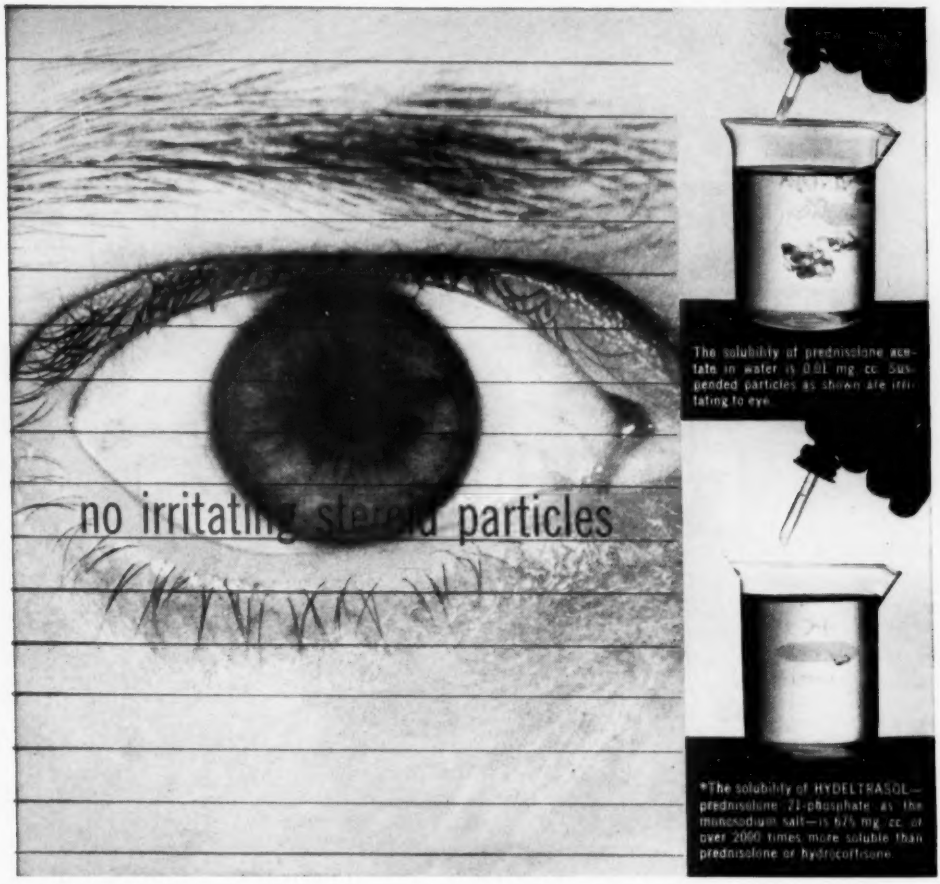
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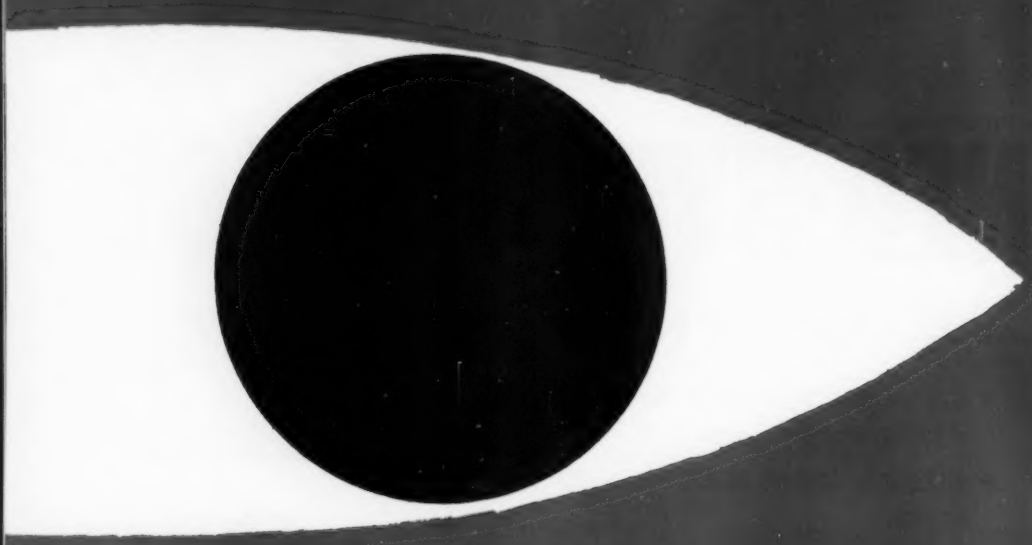

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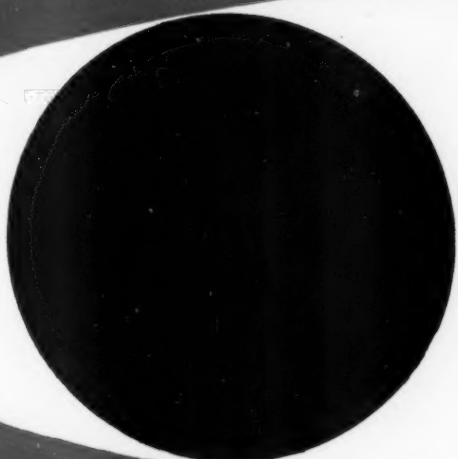
REFERENCES: (1) Perkins, E. S.: *Practitioner* 178:575, 1957. (2) Leopold, I. H.: *Arch. Ophth.* 45:44, 1951. (3) Smith, C. H.: *Eye, Ear, Nose & Throat Month.* 34:580, 1955. (4) Blakiston's New Gould Medical Dictionary, ed. 2, New York, McGraw-Hill Book Company, Inc., 1956, p. 945. (5) Ostler, H. B., & Braley, A. E.: *J. Iowa M. Soc.* 44:427, 1954.



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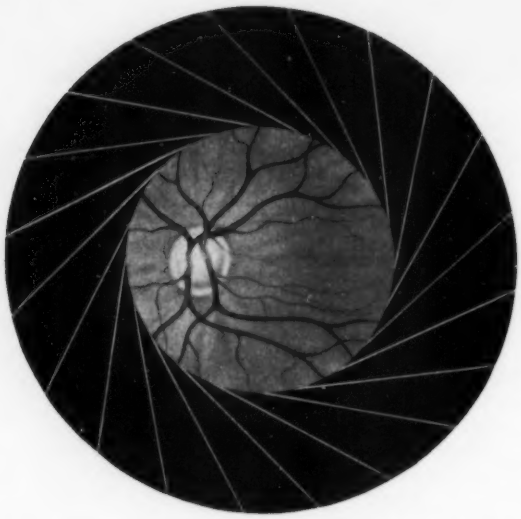

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1. Priestly, B. S.; Medine, M. M., and Phillips, C. C. To be published. 2. Ahlquist, R. P. in Drill, V. A.: Pharmacology in Medicine, McGraw-Hill Book Company, Inc. New York, 1954, p. 18-26.

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OPHTHALMOLOGY

Results of Resection of the Levator Muscle Through A Skin Incision in Congenital Ptosis

R. N. BERKE, M.D., Hackensack, N. J.

Most ophthalmologists believe that resection of the levator gives the best cosmetic and functional results in blepharoptosis. Since some surgeons prefer the external and others the internal approach, a number of operations were done through the skin and the results were compared with a previously published report [8] on resection of the levator done through the conjunctiva. This should be a fair and valid estimate of the relative merits of the two procedures because the patients were consecutive in each series and because the surgery was done at the same institution by essentially the same resident and attending surgeons.

Since Eversbusch's [1] original description, in 1883, for tucking the levator, Meller,[2] de Lapersonne,[3] Johnson,[4] Leahey,[5] and others [6-11] have described similar procedures for shortening the levator through the external route.

Material

The material for this study comprised 147 operations for resection of the levator through a skin incision on 129 patients with congenital ptosis, 10 of whom had blepharophimosis; 15, hypertropia, and 1, the jaw-winking phenomenon of Marcus-Gunn. Of the total number, 111 were unilateral and 36 were bilateral operations; 108 were primary procedures and 39 secondary. At the time of operation the youngest patient was 14 months and the oldest 32 years; the average age was 6 years 3 months. The shortest follow-up was three months (three cases); the longest, five and one-half years, and the average, one and one-half years. To simplify the analysis, patients having postnatal acquired ptosis were excluded.

Submitted for publication June 16, 1958.

Read before the meeting of the American Ophthalmological Society, White Sulphur Springs, W. Va., May 28-30, 1958.

Preoperative Examination

All patients were examined before and after operation by me to keep the records as uniform as possible and to facilitate the analysis of the data. In order to learn what type of congenital ptosis gave the best results and which the poorest, no attempt was made to exclude the unfavorable cases.

Special attention was paid to the amount of ptosis, the extraocular muscle balance, and the amount of levator action present. The amount of ptosis was estimated by noting the relative position of each upper lid with respect to each cornea in the primary position. Thus, if the right upper lid covered the right cornea 3 mm. and the left upper lid covered the left cornea 5 mm., 2 mm. of left ptosis was deemed to be present in the primary position. By this method the ptosis could be quickly and easily measured without disturbing the normal position of the lids—a complication which often occurred when the ptosis was measured by means of a ruler.

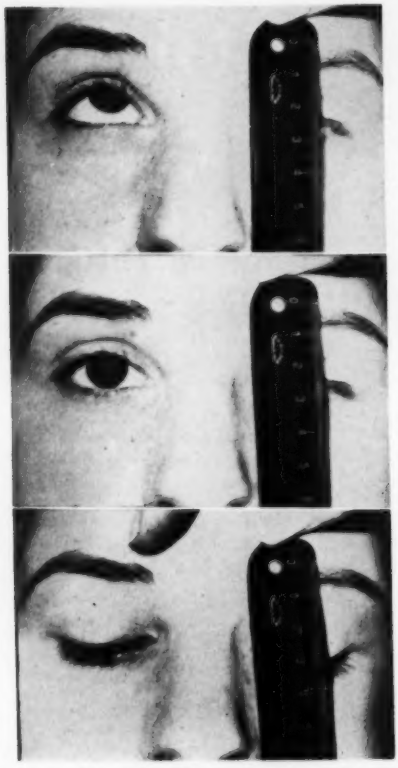


Fig. 1.—Measuring the amount of levator action. Note that the left upper lid moves up 6 mm. from a position of downward gaze to the primary position and 1 mm. more from the primary position to eyes up, making a total of 7 mm. of levator action. Figure 3B shows result of operation.

The amount of levator action was measured by holding a millimeter ruler close to the lids and noting the amount of elevation of the upper lid from a position of downward gaze to one of looking straight up while the frontalis muscle was immobilized (Fig. 1). When the amount of levator action thus measured amounted to 10 mm. or more, the levator function was considered to be excellent; when 6 to 9 mm., good; when 4 to 5 mm., fair, and when less than 4 mm., poor.

Measuring the ptosis and the amount of levator action in this way was of great practical value (as will be brought out later) because it indicated where the ptotic lid should be placed with respect to the cornea at the time of operation.

The extraocular muscle balance was examined because a weak homolateral superior rectus muscle predisposed to postoperative exposure keratitis.

Anatomy

Resection of the levator muscle is not an easy operation, mainly because the structures of the lid are thin and delicate. For example, Figure 2, copied from a cadaver specimen, shows that the thickness of the upper lid above the tarsus in this specimen is about 3 mm., into which are crowded six

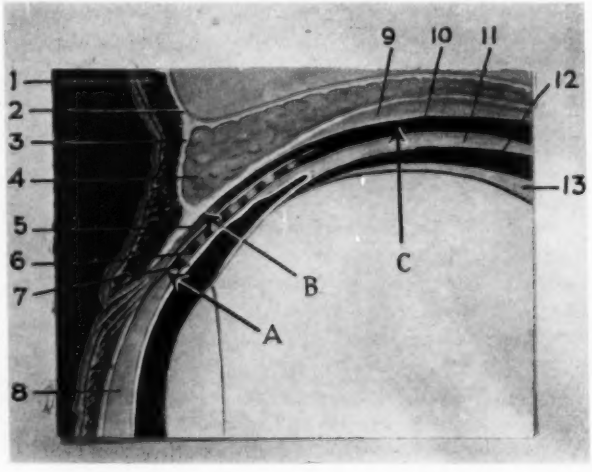


Fig. 2.—Sagittal section through upper lid and levator muscle. *1*, Orbicularis muscle; *2*, periosteum of frontal bone; *3*, septum orbitale; *4*, orbital fat; *5*, levator aponeurosis; *6*, Mueller's muscle; *7*, conjunctiva; *8*, tarsus; *9*, sheath and check ligament of levator; *10*, skeletal muscle fibers of levator; *11*, Tenon's capsule between levator and superior rectus; *12*, superior rectus muscle.

Fig. 3.—Phantom view of anatomy of upper lid to show position of ptosis clamp before cutting the levator free of the upper edge of the tarsus. Note position of the reflected tendon of the superior oblique muscle and the medial third of Whitnall's check ligament of the levator.

layers of tissue, namely, the skin, orbicularis, septum orbitale, levator aponeurosis, Mueller's muscle, and conjunctiva. Since the aponeurosis and Mueller's muscle are about 1 mm. or less in thickness, the dissection of these structures requires much care. Because Mueller's muscle usually adheres to the conjunctiva (especially in the presence of follicular hypertrophy), it tends to be reflected with the conjunctiva, thus rendering the levator too thin to support the lid.

When the upper lid is "full" and the septum orbitale joins the aponeurosis at *A* in Figure 2, it is easy to free the septum from the aponeurosis and expose the orbital fat. But when the upper lid is "thin" and the septum fuses with the aponeurosis at *B*, the levator may be perforated between *A* and *B* or the plane of dissection extended anterior to the septum toward the superior orbital margin. Both complications can be avoided by exposing the orbital fat on top of the levator before proceeding with the dissection.

The distance between *A* and *C* in Figure 2 represents the approximate amount of levator tissue to be excised in congenital ptosis with poor levator action.

Figure 3 demonstrates the position of the ptosis clamp on the aponeurosis above the tarsus and illustrates the proximity of the levator to the reflected tendon of the superior oblique muscle. Note how the medial and lateral horns and the check ligament are pulled forward by the clamp in Figure 4 after the levator has been severed from the tarsus. The dotted lines indicate where the lateral horn, medial horn, and check ligament are incised in freeing the levator from its attachments to the orbital walls. While

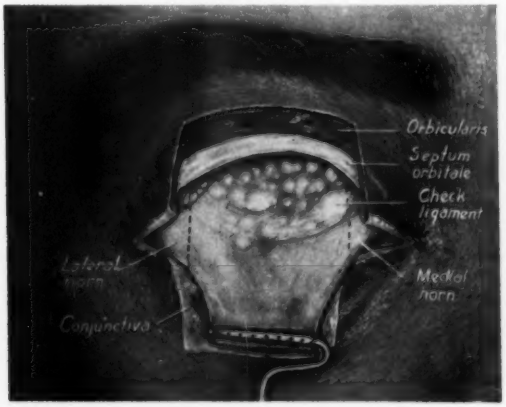


Fig. 4.—Drawing to demonstrate the restrictive action of the lateral horn, the medial horn, and the check ligament of the levator to pulling the levator forward. The levator is freed by incising these structures along the dotted lines.

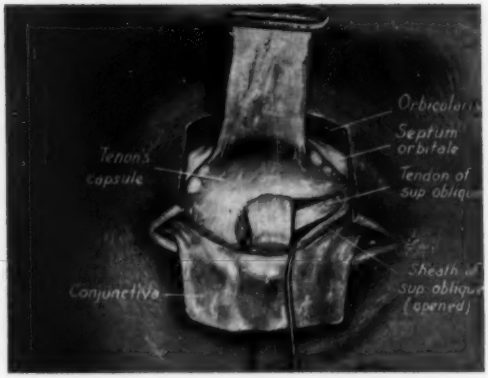


Fig. 5.—Drawing to demonstrate the relationship between the levator, Tenon's capsule, the superior rectus muscle, and the reflected tendon of the superior oblique muscle. Tenon's capsule has been opened and part of the upper lid excised to expose these structures.

the check ligament is being freed, care must be taken to avoid accidental tenotomy of the reflected tendon of the superior oblique, which lies directly beneath (Fig. 5).

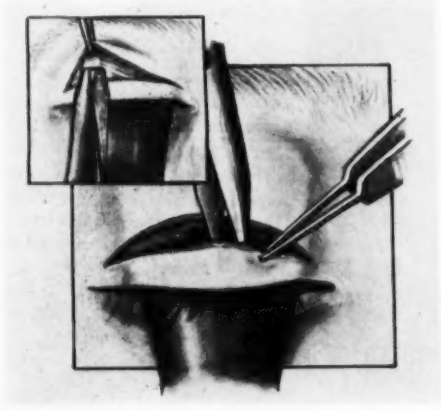
Steps of Operation

The technique employed for resection of the levator is essentially the same as that described by Johnson[4] and Leahey[5] and proceeds as follows:

1. A horn spatula is inserted in the upper fornix under the upper lid and a curved incision made through the skin and orbicularis the length of the lid 5 to 3 mm. from the lashes, after which the skin and orbicularis muscle are reflected from the tarsus almost to the lashes (Fig. 6).

Fig. 6.—After a spatula is placed under the upper lid, the skin and orbicularis muscle are incised the length of the lid and freed from the tarsus toward the lashes. The septum orbitale is then incised (insert) in the lateral third of the lid.

Figure 6



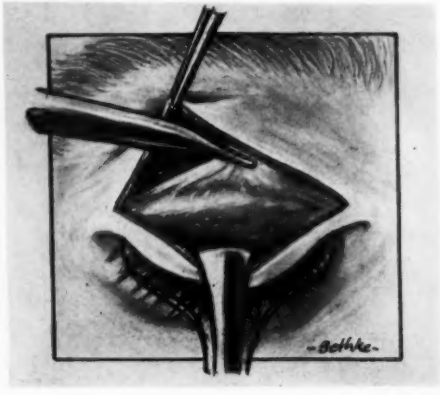
2. An Erhardt clamp is applied to the tarsus and the lid pulled down, after which the septum orbitale is opened by blunt scissor dissection (insert, Fig. 6) and cut free from the upper edge of the tarsus (Fig. 7).

3. Two stab incisions are made through the levator and the conjunctiva close to the tarsus about 20 to 25 mm. apart; a ptosis clamp is applied (Fig. 8), and both are cut free from the tarsus (Fig. 9).

4. The ptosis clamp is pulled upward and the conjunctiva carefully freed from Mueller's muscle by blunt scissor dissection, after which the conjunctiva is cut free from the ptosis clamp along the dotted line in Figure 10.

Fig. 7.—An Erhardt clamp is applied and the lid pulled down while the septum orbitale is incised close to the skin to free it from the tarsus.

Figure 7



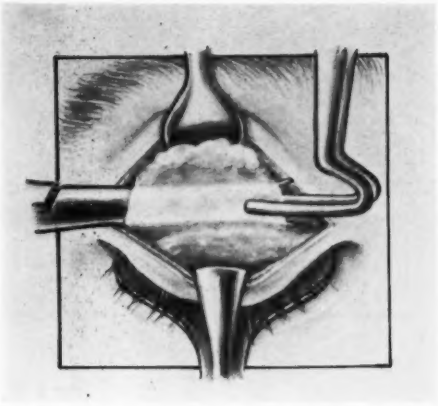


Fig. 8.—The upper skin flap is retracted upward; the levator and conjunctiva are button-holed about 25 mm. apart, and a ptosis clamp is applied.

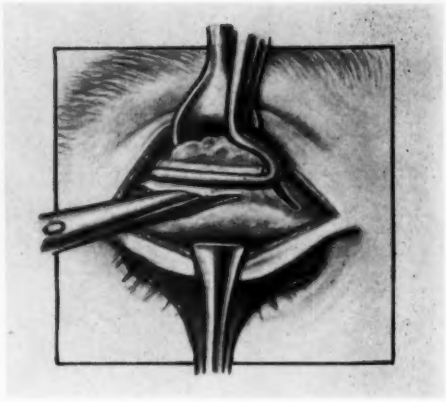


Fig. 9.—The levator and conjunctiva are cut free from the upper edge of the tarsus.

5. The levator is freed by blunt scissor dissection from Tenon's capsule for a short distance above the upper fornix (Fig. 11) and the conjunctiva sutured to the upper edge of the tarsus (Fig. 12).

6. A horn spatula is now placed under the levator (insert, Fig. 13), after which the lateral horn and the check ligament are severed (Fig. 13).

7. While the upper lid is supported at the proper height on the cornea, the levator is pulled downward over the lid and three double-armed 0000 plain absorbable surgical (gut) sutures are passed through each third of the muscle at the point where the levator crosses the upper lid margin (Fig. 14).

8. After the sutures are tied (Fig. 15), the levator is excised (insert, Fig. 15) and the sutures are passed through the superficial layers of the tarsus close to the lashes (Fig. 16) and tied.

9. After the lid has been elevated the proper amount, a second set of three 0000 plain gut double-armed sutures is passed through the upper edge of the tarsus and tied over the transplanted levator to afford a second anchorage of the muscle (Fig. 17). Then one needle of each suture is passed

Fig. 10.—The levator is pulled upward, and the conjunctiva is freed from Mueller's muscle, after which the conjunctiva is cut free from the ptosis clamp along the dotted line.

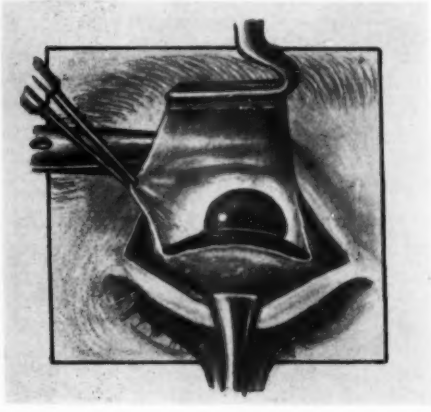
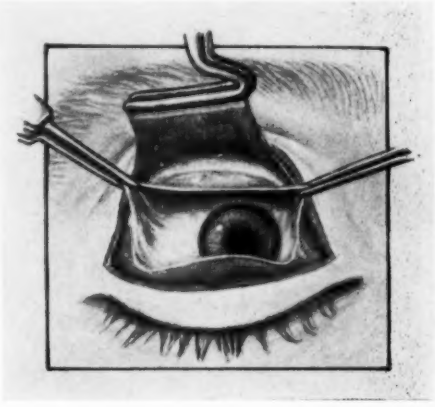


Fig. 11.—The levator is freed from the upper fornix and from Tenon's capsule for 5 to 10 mm.



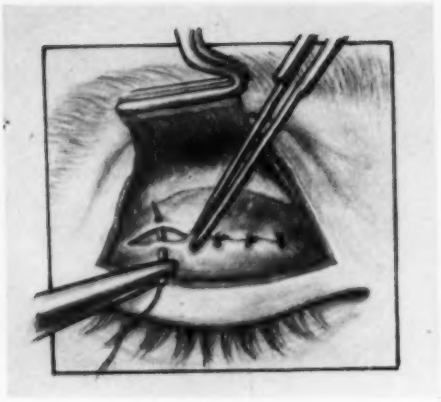


Figure 12

Fig. 12.—The conjunctiva is sutured back to the upper edge of the tarsus by 00000 plain gut surgical sutures.

Figure 13

Fig. 13.—A horn spatula is placed between the levator and Tenon's capsule while the lateral horn is incised temporally and the medial horn and check ligament nasally.

through the adjacent upper and lower skin flaps and tied again (Fig. 18) to produce an upper lid fold. Additional sutures are used to close any gaps between the skin edges, if necessary.

10. Two modified Frost sutures, tied over rubber pegs, are passed through the gray line of the lower lid and tied in the brow to pull the lower lid up to cover and protect the cornea (insert, Fig. 18).

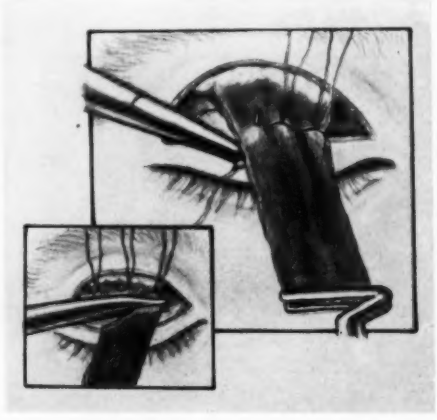
11. An antibiotic ointment is smeared over the lids; the lashes are straightened out, and a firm roller gauze pressure dressing is applied for four or five days.

Complications During Operations

Because we lacked experience with the operation, several complications occurred, many of which have been discussed in detail elsewhere.[12] Nevertheless, some of the

Fig. 14.—The upper lid is elevated manually to the proper position on the cornea, and one double-armed 0000 plain gut suture is passed through the middle third of the levator where it crosses the lid when pulled down (upper insert).

Fig. 15.—Two similar double-armed sutures are placed and tied on either side of the central suture, and the levator is excised 2 to 3 mm. anterior to the tied sutures (insert).



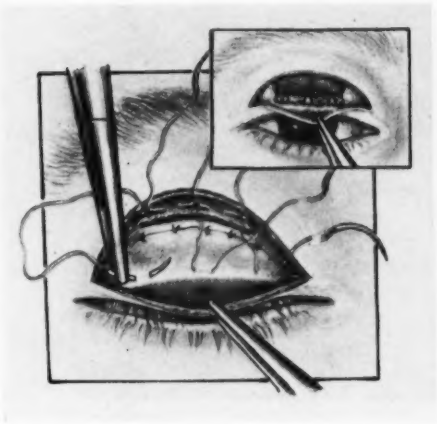


Fig. 16.—One arm of each suture is passed through the superficial layers of each third of the tarsus close to the lashes and tied to raise the lid to the proper position on the cornea.

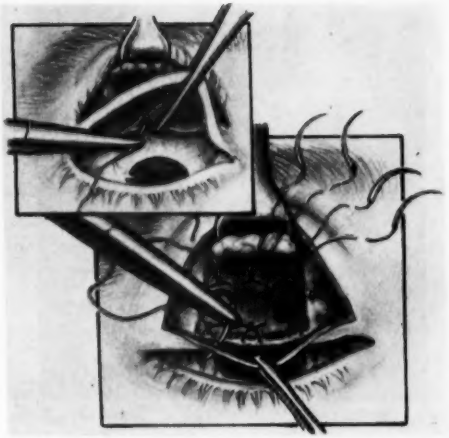


Fig. 17.—Three double-armed 0000 plain gut sutures are then passed through each third of the upper edge of the tarsus from the conjunctival surface (insert) and tied over the transplanted levator.

more frequent pitfalls and their prevention will be described here.

The initial skin incision should be accurately placed to form an upper lid fold to match that of the fellow eye. If the incision is made too high, the lashes will turn downward postoperatively (Fig. 19). If the incision is carried too deep, the tarsus or the levator may be accidentally severed; in this case the levator must be picked up on two or three hemostats and placed on a ptosis clamp so that the dissection can proceed according to plan. If a redundancy of skin is present, an appropriate elliptical piece of skin should be excised, or the skin may prolapse over the lashes postoperatively (Fig. 20). One must avoid injury to the

Fig. 18.—One arm of each suture is brought out through the adjacent upper and lower skin flaps and tied to close the skin wound and create an upper lid fold. Two modified Frost sutures are inserted through the lower lid and anchored to the brow over rubber pegs.

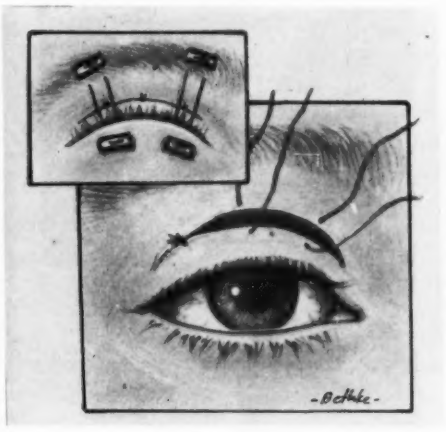


Fig. 19.—Turned-down lashes on right and fair result in presence of 4 to 5 mm. levator action. Before operation (left) and one and one-half years after (right). Both lids covered corneas 3 mm. at end of operation and 4 mm. two years later. No striated muscle fibers in biopsy specimens.

Fig. 20.—Overcorrection and redundant skin of right upper lid. Before operation (left) and 14 months after (right). A previous resection of the levator and a Hess operation had been done years before. Two millimeters of overcorrection occurred because the lid was raised to cover the cornea 2 mm. (2 mm. too high) at operation in the presence of 12 mm. levator action.

Fig. 21.—Loss of lashes of left upper lid after resection of the left levator muscle. Before second operation (left) and seven months later (right). First operation resulted in undercorrection because of insufficient resection; second operation produced good result, except for sagging of lateral third of lid. Levator action was 7 mm., and the lid was elevated to cover the cornea 2-3 mm. at end of operation. No postoperative "lift" or "fall" occurred.

roots of the lashes to prevent their permanent loss (Fig. 21).

The levator must not be injured while the septum orbitale is being severed from the tarsus. This can be avoided by piercing the septum with blunt-pointed Steven's scissors over the lateral one-third of the lid, after which the orbital fat can often be made to prolapse through the perforated septum by exerting backward pressure on the globe. The septum should be cut free from the tarsus close to the edge of the upper skin flap to avoid injury to the underlying levator tendon.

While dissecting the conjunctiva one may unintentionally free it from the sclera down to the limbus, causing the upper fornix to prolapse over the upper cornea postoperatively. This complication can be avoided by tying a surgical gut suture in the tendon of the superior rectus muscle before starting the operation or by anchoring the upper fornix to the superior rectus muscle later.

While incising the lateral horn, one often encounters several small lobules of the accessory lacrimal gland, which can be excised with impunity. However, excision of the main lobe of the gland should be avoided

Fig. 22.—Overcorrection of ptosis and lagophthalmos in eyes down due to "band-to-pulley." Lagophthalmos in eyes down (left) and improvement after operation (right). After the band was excised through a skin incision, the lagophthalmos and overcorrection were less.

by cutting the horn 4 to 5 mm. from the lateral orbital wall.

The check ligament extends across the levator from the pulley to the main lobe of the lacrimal gland and blends with the underlying sheath of the reflected tendon of the superior oblique nasally. Because of this relationship, one may accidentally sever the superior oblique tendon while freeing the levator. This complication can be avoided by placing a spatula between Tenon's capsule and the levator muscle close to the pulley while cutting the check ligament. If the ligament is not completely freed, a notch in the nasal one-third of the upper lid may develop when the patient looks down postoperatively (Fig. 22).

After the lateral horn and the check ligament have been severed, the levator can be pulled forward for 10 to 20 mm. unless the septum is still attached to it, in which case some strands of this membrane can always be felt extending from the ptosis clamp to the superior orbital margin. These must be freed or the septum will be resected along with the levator, causing the lid to be anchored to the superior orbital margin and producing lagophthalmos in downward gaze.

Adhesions between the levator and the superior rectus muscle are usually easily broken by blunt scissor dissection, but if a previous resection of the levator has been done, they may have to be cut by means of scissors. After this, one should be able to move the globe freely up and down manually without transmitting movement to the levator.

If insufficient levator tissue has been excised the lid will cover the cornea too much, in which case the levator must be tucked or additional tissue excised. However, if too much levator tissue has been removed, the levator will be too short to reach the tarsus. This embarrassing error can be avoided by having the assistant support the lid on the cornea at the desired level while the surgeon pulls the levator down over the lashes. The point of crossing marks the site for placing the sutures, after which the excess levator tissue can be excised without fear of cutting the muscle too short.

If the tarsus becomes markedly everted after the first set of sutures is tied, this condition will be remedied after the second set of sutures has been placed. A small amount of ectropion will correct itself when the tone of the orbicularis returns. Before the pressure dressing is applied, the lashes must be turned upward to prevent irritation of the cornea and distortion of the lashes postoperatively. If the Frost sutures indent the skin of the upper lid, a small roll of cotton should be placed under them. The dressing must give uniform pressure to the lids; otherwise, pressure necrosis with loss of the lashes or the lid margin may occur.

Postoperative Complications

If the pressure dressing has been correctly applied, very little edema will be present, the cornea will be clear, and the lashes will be in good position when the dressing and the Frost sutures are removed on the fourth or fifth postoperative day.

If the ptosis has been fully corrected, lagophthalmos will be present in sleep, especially if the levator action is poor or if the superior rectus is weak. In either case, the cornea must be protected against drying at night. Pulling the lower lid up over the cornea during sleep (preferably by strips of cellophane tape) affords excellent protection for the cornea. During the day the cornea is protected against drying by hourly instillations of methylcellulose (½% to 1%) eye drops. This simple routine will prevent serious exposure keratitis.

If the upper fornix prolapses over the cornea, it will usually recede spontaneously in a few weeks if small; if large, it will have to be replaced or excised. Occasionally an induced weakness of the superior rectus will be present soon after the operation, but this complication usually disappears in a few weeks.

If the reflected tendon of the superior oblique was accidentally severed during the operation, overaction of the homolateral in-

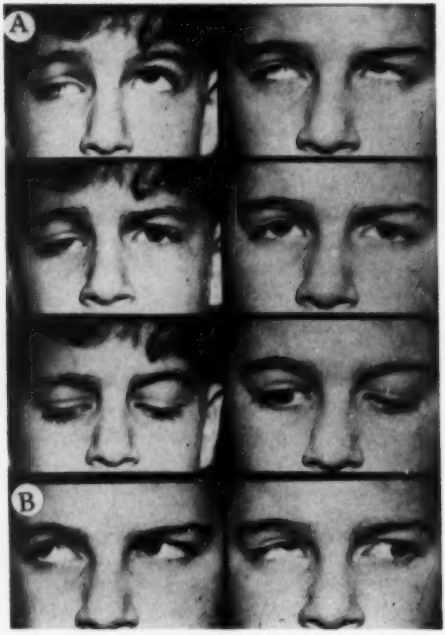


Fig. 23.—Overaction of right inferior oblique caused by accidental tenotomy of right superior oblique. *A*, before operation (left) and one and one-half years after (right). *B*, eyes right and eyes left. Levator action 8 mm. Lid covered cornea 3 mm. at end of operation.

ferior oblique may occur (Fig. 23). This complication is best treated by a large myectomy or recession of the overacting inferior oblique muscle.

Occasionally overcorrection of the ptosis may be associated with retraction of the lid in abduction or downward gaze (Fig. 22). In such cases, a band of tissue can be felt extending from the nasal third of the lid to the pulley of the superior oblique muscle. This complication occurs because the check ligament has not been completely freed or because the sheath of the superior oblique tendon has been accidentally incorporated in the sutures placed in the levator.

Results of Resection of Levator Through Skin Approach

In order to learn when the operation was indicated and when not, all types and degrees of congenital ptosis were subjected to operation. This course of action was justified because some authors [14,15] believe that resection of the levator will give an excellent result, even when little preoperative levator action is evident.

To simplify the analysis, the 147 operations were divided into 108 primary and 39 secondary procedures.

Results in 108 Primary Operations.—For the 108 primary operations the average amount of ptosis before operation was 4.1 mm.; the average amount of correction, 3.4 mm., and the average amount of residual ptosis, 0.7 mm. To learn what effect weakness of the homolateral superior rectus muscle had on the final result, the 108 cases were divided into 93 patients with normal and 15 with weak superior rectus muscles and the results of operation compared. This appraisal showed that there was little or no difference in the amount of ptosis or in the amount of correction achieved for the two groups. Therefore, weakness of the superior rectus muscle was not a bad prognostic sign for resection of the levator through the skin route.

Results in Thirty-Nine Secondary Operations.—In 39 patients the levator was resected to correct a residual ptosis, 31 of which had had a previous resection of the levator; 3, an unsuccessful frontalis operation, and 5, some type of Motais-Parinaud procedure.

For the 31 patients subjected to a previous resection of the levator, the average preoperative ptosis was 3.1 mm.; the average correction, 3.1 mm., and the average residual ptosis, 0 mm. From this analysis it is clear that a second resection of the levator is often successful, even though the first failed.

In the three instances where a previous frontalis operation had been done, the dissection was only slightly more complicated by the formation of scar tissue induced by the previous operation. However, when a previous Motais-Parinaud operation had been done, the operation was much more difficult, owing to the extensive adhesions between the levator and the superior rectus muscle. Since only three of these eight

TABLE 1.—*Effect of Superior Rectus Function on Amount of Correction for the Internal and External Procedures (Primary Operations)*

Type of Operation Done	Function of Superior Rectus	Operations, No.	Average Amount of Ptosis, Mm.		
			Before Operation	After Operation	Improvement
Internal	Normal	57	3.6	1.2	2.4
External	Normal	93	4.1	0.6	3.5
Internal	Weak	21	4.4	2.3	2.1
External	Weak	15	4.1	0.8	3.3

secondary procedures resulted in full correction of the ptosis, better results may have occurred if all eight lids had been suspended from the brow.

TABLE 2.—*Amount of Correction After the Internal and External Procedures (Secondary Operations)*

Type of Operation Done	Operations, No.	Average Amount of Ptosis, Mm.		
		Before Operation	After Operation	Improvement
Internal	6	4.0	1.7	2.3
External	31	3.1	0	3.1

Relative Merits of Internal and External Operations

When the results for the 78 internal and the 108 external operations were compared, the latter produced over 1 mm. greater average correction, whether the superior rectus was weak or normal (Table 1). The same was also true to a smaller degree for the secondary procedures (Table 2). Therefore, the anterior approach for resection of the levator always gave a greater amount of improvement in congenital ptosis than did the posterior method.

TABLE 3.—*Final Results After the Internal and External Procedures (Primary Operations)*

Type of Operation	Cases, No.	Over-corrected, %	Fully Corrected, %	Under-corrected, %
Internal	78	0	39.7	60.2
External	108	19.4	39.8	40.7

The percentage of full correction for the internal and the external operations was essentially the same, being 39.7% and 39.8%, respectively (Table 3). Furthermore, the external produced about 20% fewer undercorrections and about 20% more overcorrections than the internal procedure. From this it would seem that whatever advantage was gained for the external method by fewer undercorrections was lost by a greater number of overcorrections produced. But, since these overcorrections could be prevented (as will be shown later) and since undercorrection could not be overcome by the internal procedure, it would seem that the relative merits of the two operations weigh heavily on the side of the external approach.

Results in Bilateral Ptosis

There were 36 bilateral operations, of which 32 were primary and 4, secondary procedures. When the ptosis was equal or almost equal, both sides were operated upon at the same time, with the hope that both lids would be equally corrected when healing was complete if both were elevated to the same position on the cornea at the time of operation. However, this worthy objective was achieved in only nine patients (18 eyes).

In some cases where the levator action and the ptosis were essentially the same on both sides it was impossible to elevate both lids to the same level at operation because the levator muscles were not equally de-

TABLE 4.—*Effect of Operation on Unilateral and Bilateral Ptosis (Primary Operations)*

Type of Ptosis	Operations, No.	Average Levator Action	Average Amount of Ptosis, Mm.			Over-corrected, %	Fully Corrected, %	Under-corrected, %
			Before Operation	After Operation	Improvement			
Unilateral	76	5.9	4.4	0.9	3.5	21.5	37.5	41
Bilateral	32	4.5	5.1	1.6	3.5	10	35.0	55

Fig. 24. — Overcorrection of the right ptosis and droopiness of the unoperated left upper lid 10 months after operation. Before operation (left), 10 months after (center), and final result (right). A previous resection of the levator had been done 10 years before. Note that the left upper lid is lower on the cornea 10 months after operation on right lid. This was corrected later by a tenotomy of the right and a resection of the left levator muscle, with a good final result.

veloped. In other cases one lid would "fall" postoperatively more than the other, and so a unilateral ptosis of 2 mm. or more often persisted.

Because the ptosis was greater and the levator action less, the average results for the bilateral operations were not as good as those for the monocular cases, even though the amount of correction was the same in each (Table 4).

Some patients with binocular unequal ptosis presented a problem when surgical correction of the more ptotic lid resulted in an apparent overcorrection, even though the corrected lid covered the cornea a normal amount (2 mm.) in the primary position (Fig. 24). In a few of these cases the other lid was subsequently elevated also to affect a satisfactory result. In such patients one should anticipate this result and warn the parents of the possible need for correcting the less ptotic lid later.

Effect of Levator Action on Amount of Ptosis Before and After Operation

Chart 1 shows that the amount of preoperative ptosis varied inversely with the amount of levator action present. For example, when the levator action averaged 2.5 mm., the preoperative ptosis measured 6.6 mm., but when the levator action averaged 11 mm., the ptosis was only 2.8 mm. Consequently, the amount of preoperative ptosis depended on the amount of levator action present.

The amount of postoperative ptosis was also governed by the levator function, because when the levator action averaged only 2.5 mm., the residual ptosis was 2.5 mm., but when the levator action was 11 mm., the ptosis was overcorrected an average of 0.3 mm. Therefore, the levator action determined the amount of ptosis after operation also—the ptosis being more marked when the levator was poor and less or absent when it was good.

Since the lines in Chart 1 representing the amount of ptosis before and after operation are roughly parallel, it is obvious that the amount of correction achieved by operation averaged 3.5 mm., regardless of the amount of preoperative levator action present.

Effect of Levator Action on Overcorrection and Undercorrection

The amount of levator function played a dominant role in determining the number of postoperative overcorrections. For example, when the levator action averaged 2.5 mm., none of the 108 primary operations were overcorrected, but when it averaged

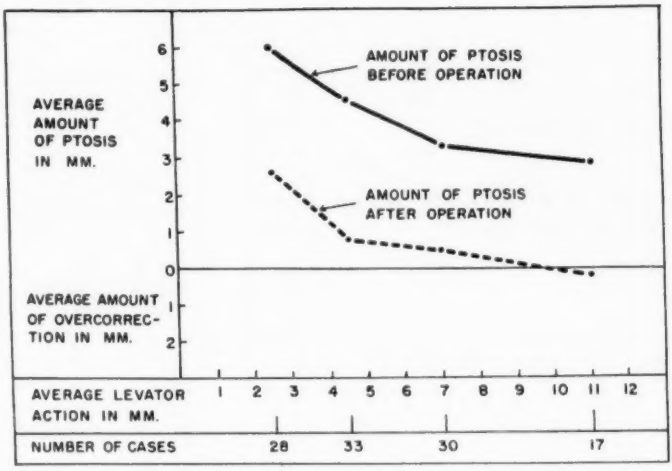


Chart 1.—Effect of levator action on amount of ptosis before and after operation.

11 mm., 53% were overcorrected (Chart 2). Hence, overcorrection never occurred when the levator action was poor.

The degree of levator function also affected the number of undercorrections, because when the levator action was 2.5 mm., 82.1% were undercorrected, compared with only 6% when it was 11 mm. (Chart 2). Therefore, undercorrection rarely occurred when the levator action was good.

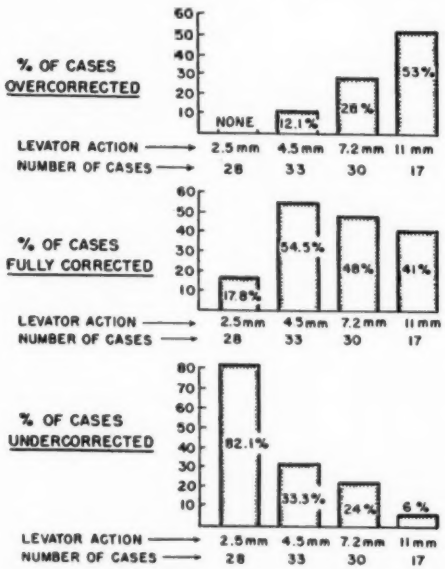


Chart 2.—Effect of levator action on final result in 108 primary operations.

Likewise, the number of overcorrections and undercorrections for the 39 secondary operations depended on the amount of levator action, because when the levator function averaged 3 mm., none of the lids were overcorrected, but when it was 7.6 mm., 40% were overcorrected (Chart 3). Hence, overcorrection never occurred in the presence of poor levator action, after a secondary resection of the levator.

Moreover, when the levator action was poor, 72.7% of the secondary procedures were undercorrected, but when it was good, only 5% had a residual ptosis (Chart 3). Thus, undercorrection was also rare after a secondary resection of the levator when the levator function was good.

From these data it is clear that the amount of preoperative levator action was a significant factor in determining the final result of operation for both the primary and the secondary operation.

Effect of Levator Action on Amount of "Lift" or "Fall" of Lid After Operation

The final position of the lid after operation depended mainly on two factors: the amount of levator action present and the position of the lid at the end of operation. Thus, when the levator action was poor (2.5 mm.), none of the lids "lifted" after operation, but when the levator function

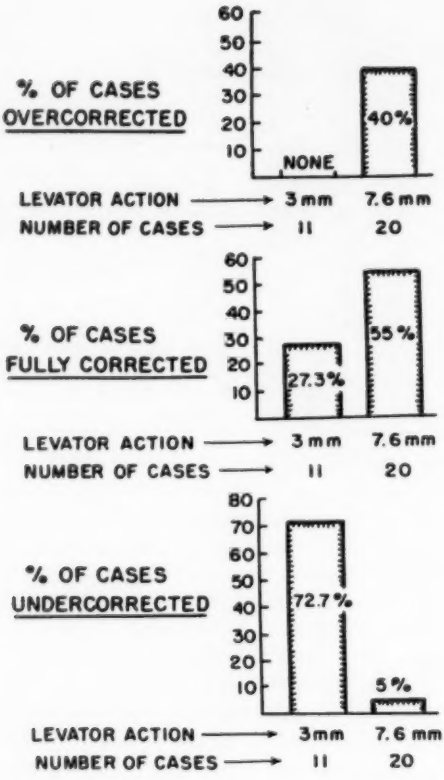


Chart 3.—Effect of levator action on final result in 31 secondary operations.

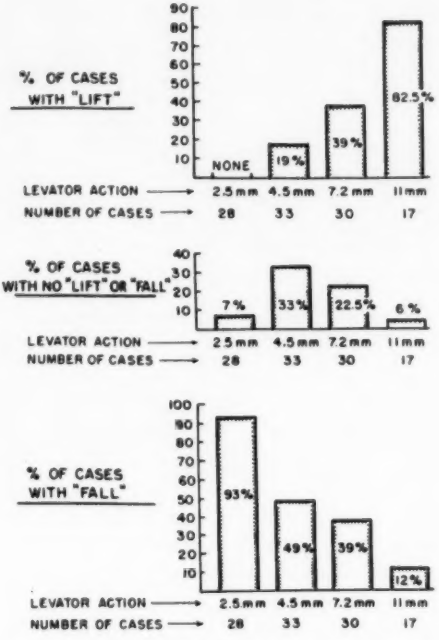


Chart 4.—Effect of levator action on postoperative "lift" or "fall" in 108 primary operations.

was good (11 mm.), 82.5% did so (Chart 4)—that is to say, the lids were higher with respect to the cornea when healing was complete than they were at the end of operation. Furthermore, when the levator action was poor 93% registered a "fall," compared with only 12% when the levator action was good. Thus, the final position of the lid depended very much on the amount of levator action present.

These observations were of great practical importance because the surgeon had to compensate for the "lift" or "fall" by undercorrecting the ptosis when the levator action was good and overcorrecting when it was poor.

But how much should the ptotic lid be over- or undercorrected? The answer depended on the amount of levator action present. For example, when the levator action averaged only 2.5 mm., the average lid "fell" 2.6 mm., but when the levator function was 11 mm., the average lid "lifted" 1.3 mm. (Chart 5). Furthermore, when the levator action averaged 4.5 mm., the amount of "fall" was only 0.5 mm., and when it measured 7.2 mm., no "lift" or "fall" occurred on the average.

Since the amount of "lift" increased as the amount of levator action increased, it would seem that all overcorrections could have been prevented by intentionally undercorrecting the ptosis to compensate for the "lift" when the levator action was good. Also, since the amount of "fall" increased as the amount of levator action decreased, it would seem that all undercorrections could have been avoided by lifting the lids higher on the cornea at operation to compensate for the "fall" which usually occurred when the levator action was poor. But this is not a valid conclusion, because the gross structure of the levator was often

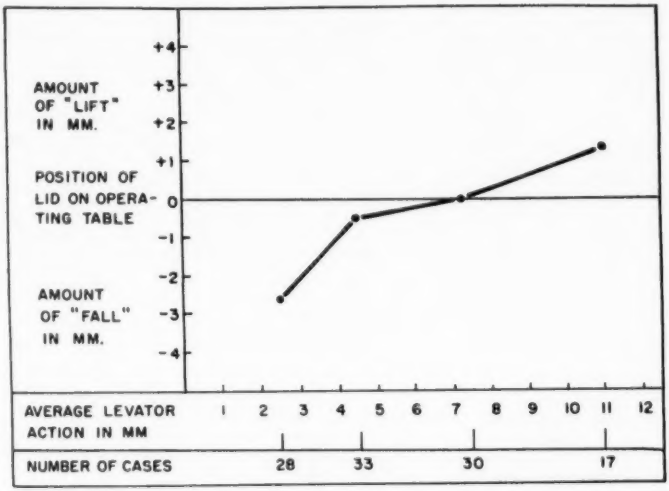


Chart 5.—Effect of levator action on amounts of "lift" or "fall" of the lid after operation.

too thin to support the lid fully and even when the levator was adequate structurally to lift the lid the appropriate amount the final result often was undercorrection, owing to the tendency of such levators to stretch with time. Nevertheless, it is certain that the number of undercorrections could have been reduced by overcorrecting the ptosis the proper amount in patients with poor levator action.

Effect of Striated Muscle Fibers on Levator Action

In a previous paper,[13] it was shown that the amount of preoperative ptosis and the amount of correction achieved by operation depended on the number of striated muscle fibers found in the levator biopsy specimen. The present report not only confirms the previous observations but also shows that the amount of preoperative levator action seemed to depend on the number and nature of such fibers seen histologically. For example, Chart 6 shows that when the levator action averaged 2.5 mm., only 7% of the specimens demonstrated striated muscle fibers, but when the levator action averaged 11 mm., 75% did so. (In some cases with good levator action a short specimen was intentionally excised to avoid overcorrection. Had more levator tissue been removed in these cases, doubtless the percentage of striated muscle fibers would have approximated 100%). Also, it should be added that the number of normal-appearing striated muscle fibers was always greater when the levator action was good. Hence, the amount of levator action depended primarily on the number and nature of the striated muscle fibers present; since the percentage of good results varied directly with the amount of levator action, the number of striated muscle fibers must have been the basic factor responsible for the amount of correction achieved.

Effect of Gross Structure of Levator on Final Result

The gross appearance of the levator at operation varied somewhat with the amount of levator action and the number of striated muscle fibers present but was not a reliable guide as to the final result. For example, Chart 6 shows that 28% of the patients with poor (2.5 mm.) levator action had what was described at operation as "good" levator tissue, but, since over 75% of these were undercorrected despite the presence of "good" levator tissue, it is obvious that one cannot judge how much to overcorrect these cases on the basis of the gross appearance of the levator alone. Hence, even though

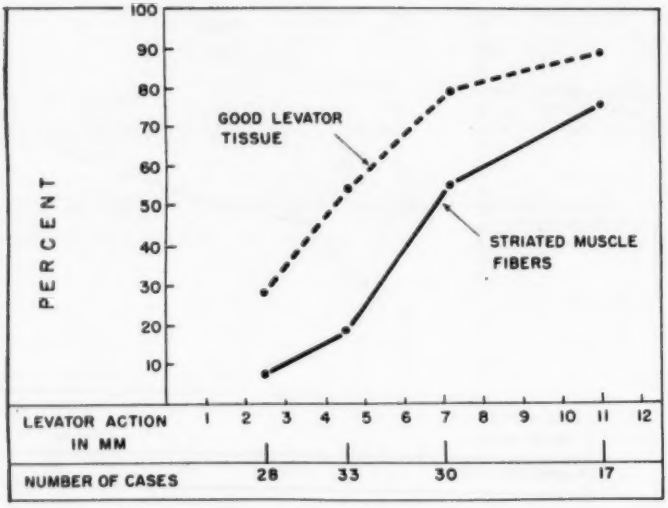


Chart 6. — Effect of levator tissue and striated muscle fibers on amount of levator action.

the levator appeared to be strong enough to correct the ptosis fully, the success of the operation was generally short-lived, owing to the tendency for such levators to stretch with time.

Since only 5% of these "good" levators had striated muscle fibers when the levator action was poor and since most of these cases were undercorrected, it would seem that the success of this operation depended on the number of contractile striated muscle fibers and the amount of levator action present but not on the gross appearance of the levator.

Because Mueller's muscle was always present, the levator usually appeared to be of good consistency above the tarsus. However, it was usually impossible to appraise the gross structure of the striated muscle portion of the levator until it had been completely freed from its several attachments. When the exposed levator was adequate to correct the ptosis, the lid was elevated to its predetermined position on the cornea and the operation completed in the usual manner. But when the levator was too delicate to support the lid, resection of the levator was abandoned and the lid was

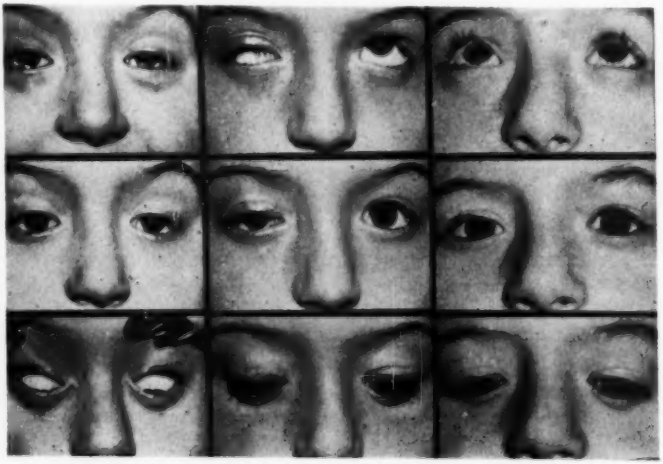


Fig. 25.—Poor result on right and good result on left lid after bilateral resection of the levator. Before bilateral levator resection (left), six months later (center), and after suspension of right lid from superior rectus (right). Levator action was 5 mm. on right and 4 mm. on left. Right levator was too thin to support the right upper lid at time of second resection of levator. Therefore, it was suspended from the superior rectus muscle with a fairly good result.

supported from the superior rectus (Fig. 25) or from the brow. In this way a second operation for ptosis was avoided.

Effect of Operation on Amount of Levator Action

Of 49 cases in which a record was kept of the amount of levator action present before and after operation, 43 had from 1 to 7 mm. (average 2.2 mm.) more levator action after than before the operation. These figures would tend to substantiate the claims of de Blaskovics [14] and others that resection of the levator does in fact increase the amount of levator function. This observation may also explain why the average amount of ptosis for the secondary operations was about 1 mm. less than for the primary procedures and why secondary operations produced a higher percentage of full corrections than did the primary procedures.

Effect of Suture Material on Final Result

Various kinds of surgical gut sutures were used with equivocal effects on the final result. After using 0000 plain gut, 0000 chromic gut, and 00000 chromic gut sutures, it was decided that the plain gut sutures were the best because they lasted four to eight days (average, five days) and caused less reaction than the chromic gut sutures. The 0000 chromic sutures lasted 7 to 15 days (average, 11 days), and the 00000 chromic sutures persisted from 6 to 16 days (average, 8 days), both of which remained longer than necessary. Because the levator was sandwiched between the tarsus and the orbicularis and anchored there by two sets of sutures, it was difficult for the levator to pull loose from the lid during the healing process, even though some sutures were absorbed before the fifth postoperative day.

Effect of Trial and Error on Final Result

Since we did not realize at the start the importance of overcorrecting the ptosis when the levator action was poor and undercorrecting it when the levator action was good, our early results were very erratic and unpredictable. For example, Chart 7 shows that the percentage of overcorrections gradually decreased over a six-year period from 30% for the first 20 cases to only 15% for the last 20, while the undercorrections declined from 40% to only 20% and the full corrections improved from 30% to 65% over the same period. Furthermore, the amount of overcorrection and undercorrection was also much reduced, so that if 1 mm. of over- or undercorrection is acceptable, a satisfactory result was achieved in about 90% of the last 25 patients. This high percentage of satisfactory corrections was obtained only after we had learned by trial and error to overcorrect the ptosis when the levator action was poor and to undercorrect it when the levator action was good.

Cause and Treatment of Undercorrection

When undercorrection occurred in the presence of good levator action, the commonest cause was insufficient resection, but when undercorrection was associated with poor levator function, the commonest cause was poor levator tissue. Poor technique contributed to some undercorrections. Failure of the sutures and postoperative edema were infrequent causes for undercorrection.

Since only 5% of the secondary operations resulted in undercorrection in the presence of good levator action (Chart 3), it would seem that a second resection of the levator should be done when a residual ptosis persists and the levator action is good, but since only 27.3% of the secondary operations resulted in full correction when the levator action was poor, a second resection in such cases should be abandoned in favor of some other type of ptosis operation.

Cause and Treatment of Overcorrection

When overcorrection occurred the cause was usually resection of too much levator tissue or the formation of a band of tissue extending from the lid to the pulley. The

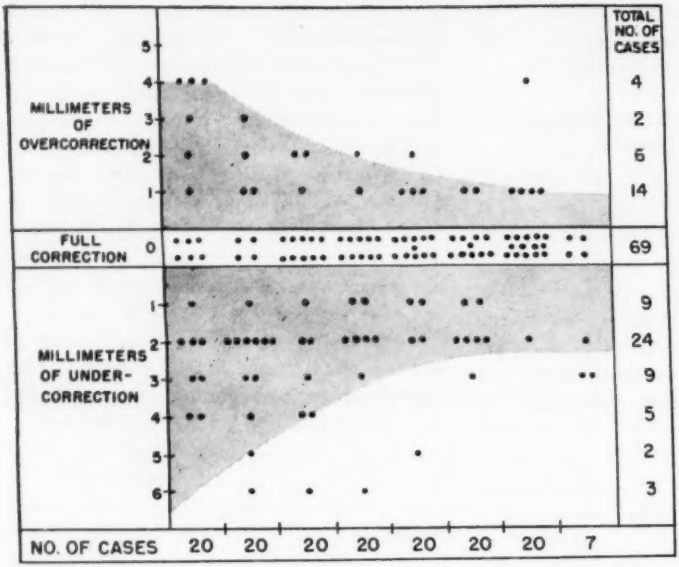


Chart 7.—Effect of experience on final result of 147 operations.

latter was remedied by excising this band through a skin incision.

When 2 mm. or more of overcorrection was caused by too much resection, the levator was tenotomized through a conjunctival incision in eight cases, with improvement in all. The operation is simple to perform and can be done in adults in the office under local anesthesia. The lid is everted on an Erhardt lid clamp and an incision made through the length of the tarsus 1 mm. from its upper edge and extended into the

Fig. 26—Tenotomy of the levator. The lid is everted and the tarsus incised the length of the lid 1 mm. from its upper edge. The incision is deepened into the pretarsal tissues until the edges of the wound open up to at least twice the amount of overcorrection. The conjunctiva is not sutured. An intermarginal suture is left in place for several days.

Figure 26

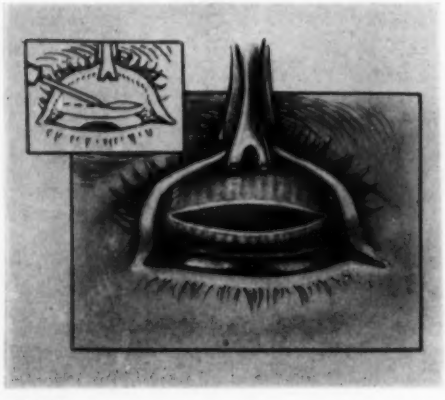


Fig. 27.—Excellent result. Before operation (left) and seven months after (right). Levator action 11 mm. Left upper lid raised to cover cornea 6 mm. at end of operation. Note absence of ptosis in eyes up and minimum lagophthalmos in eyes down. Striated muscle fibers found in biopsy specimen.

Figure 27

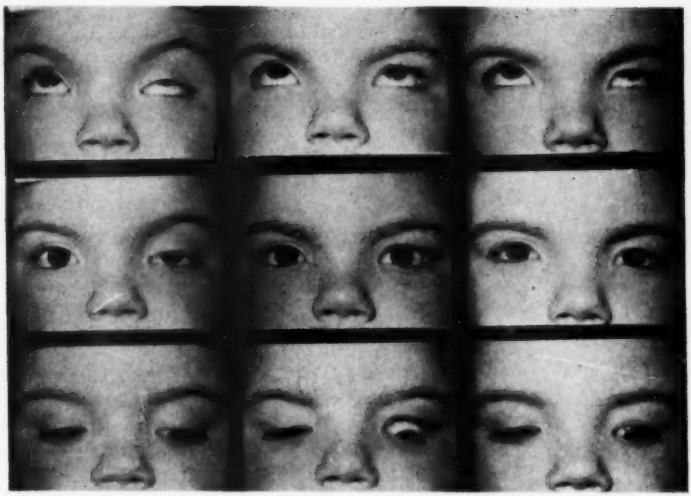


Fig. 28.—Excellent result with only 4 mm. of preoperative levator action. Before operation (left) one week after (center), and 10 months after (right). Left upper lid raised to limbus at operation. Ten months later it covered cornea 2 mm. in primary position. Note how much of the lagophthalmos in eyes down disappeared 10 months after operation. Also note slight left ptosis in eyes up. This is characteristic of poor levator action.

pretarsal tissues until the edges of the wound expand to at least twice the amount of overcorrection present. No sutures are used to close the wound (Fig. 26). One intermarginal suture is inserted and left in place for three to four days to prevent the cut edges of the tarsus from growing together again. If necessary, the operation can be repeated.

Prevention of Overcorrection and Undercorrection

Since overcorrection occurred most often in the presence of good levator action and since such lids nearly always "lifted" after operation, overcorrection could have been avoided by undercorrecting such cases an appropriate amount. Since undercorrection occurred most often when the levator action was poor and since most of these lids "fell" after operation, undercorrection could have been prevented by overcorrecting such lids the proper amount. Thus, when the levator action was good (10 to 12 mm.), the ptosis should have been undercorrected at least 2 or 3 mm.; when the levator action measured 6 to 8 mm., the ptosis should have been fully corrected, and when the levator action was as poor as 2 or 3 mm., the ptosis should have been overcorrected 2 to 3 mm. However, overcorrection of the ptosis on the table in all patients with poor levator action is sometimes, as stated above, an im-

Fig. 29.—Excellent result in bilateral ptosis with only 4 mm. levator action of each lid. Before operation (left) and five months after (right). Each lid covered each cornea 2 mm. at end of operation and 4 mm. five months later. No striated muscle fibers found in either biopsy specimen.

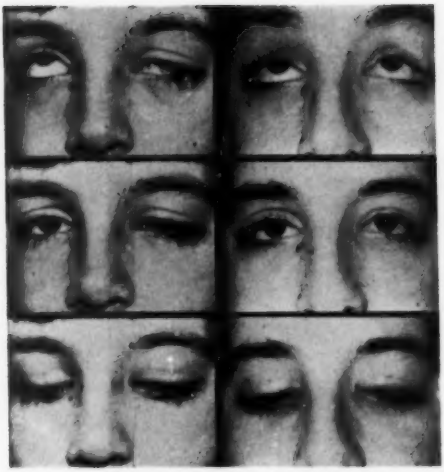


Fig. 30.—Good result from resection of levator through skin after a previous resection through the conjunctiva 10 years before. Before operation (left) and nine months after (right). Levator action was 8 mm. Left upper lid covered cornea 4 mm. at end of operation and 2 to 3 mm. nine months later.

possibility, owing to the poor levator tissue present.

Illustrative Case Reports

Because pictures tell their story better than a volume of description, a number of photographs of different types of congenital ptosis are presented, with a brief description of the most pertinent clinical and operative data to illustrate the diverse nature of con-

Fig. 31.—Excellent result after two previous ptosis operations in Argentina. Before operation (left) and 13 months after (right). Levator action was 6 mm. on one occasion and 4 mm. on another. Lid covered cornea 2 mm. at end of operation and 1.5 mm. when last seen, 16 months later. A few striated muscle fibers found in biopsy specimen.

genital ptosis and some of the problems concerning its surgical correction (Fig. 28 to 43).

Summary

In order to determine which method for resection of the levator—the internal or the external approach—gives the best results, a series of 147 operations for congenital ptosis, with use of the skin route, are analyzed and the results compared with a similar series done through the conjunctiva. Since the cases were consecutive in each group and were done by essentially the same surgeons, it is believed that this comparison of the relative merits of the two procedures is a fair and valid one.

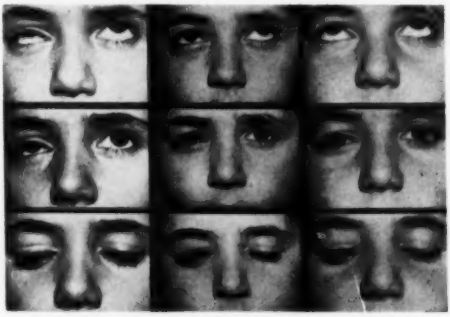


Fig. 32.—Good result after third resection of the levator. After second operation (left), two months after third operation (center), and six months after third operation (right). Note that the right hypotropia in eyes up two months after operation had disappeared four months later. Levator action 6 mm. before first operation and 10 mm. before third.

The anatomy of the lid is reviewed, and the steps of the operation are described. The complications during and after the operation are enumerated, and their prevention is explained.

Of 147 external operations done, 108 were primary and 39 were secondary procedures. The average amount of correction for each group was the same, being 3.5 mm., and the percentage of full corrections was also essentially the same, being 39.8% and 42%, respectively. Therefore, the prognosis for a satisfactory result was just as good for the second as for the first operation.

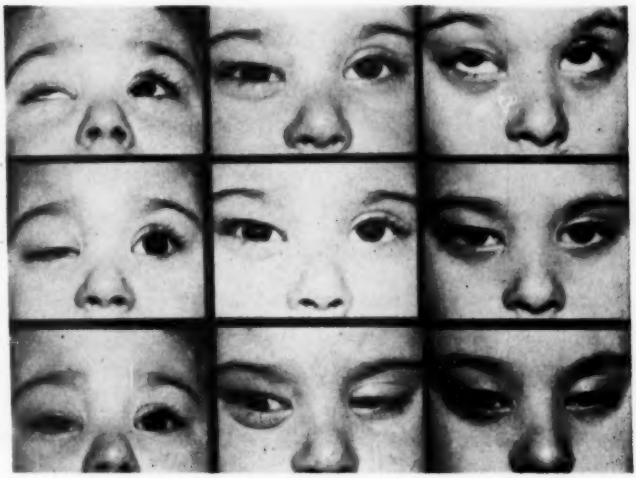


Fig. 33.—Four millimeters of overcorrection due to too much resection and formation of a "band-to-pulley." Before operation (left), three months after (center), and three years after (right). Levator action 6 mm. Left upper lid raised to 2 mm. above the limbus at operation under the theory the lid would "fall" 4 mm. later. The band to the pulley was excised and the levator tenotomized to remedy the overcorrection. A piece of skin should have been excised from the lid also. The redundant skin of right upper lid covers up the overcorrection three months after operation.

The prognosis for full correction was always good for the primary and secondary operations when the levator action averaged more than 7 mm. and always poor when it averaged only 2.5 mm.

When the homolateral superior rectus muscle was weak, the amount of correction achieved by operation was essentially the same as when the superior rectus was normal—the amount of correction being 3.3 mm. and 3.5 mm., respectively. Thus, a weak superior rectus muscle was not a bad prognostic sign for resection of the levator by the skin route.

The results of resection of the levator through the external approach were on the average better for the monocular than for the binocular cases, mainly because the ptosis was greater and the levator action less in the latter.

Fig. 34.—Marked overcorrection from resection of too much levator tissue. Before operation (left), two years eight months after (center), and seven months after tenotomy (right). A previous Blaskovics ptosis operation had been done three months before. Levator action measured 10 mm. Left upper lid raised to 2 mm. above the limbus at operation, where it remained 33 months later when a buttonhole tenotomy of the levator was done through a skin incision. Note keloid formation in left upper lid fold.

Fig. 35.—Before operation (left), two weeks after (center), and eight months after (right). Before operation the left levator action measured 7 to 8 mm. (Fig. 1). The left lid covered the cornea 5 mm. in the primary position before operation, 3 mm. at the end of operation, 4 mm. two weeks later, and 1 mm. eight months later. Thus, the left lid elevated 2 mm. in eight months from its position on the operating table to give 2 mm. of overcorrection.

When the external and the internal operations were compared, the average amount of correction for the former exceeded the latter by 1.1 mm. for the primary and 0.8 mm. for the secondary operations. Therefore, since the external always gave a greater average amount of correction than the internal method, it would appear to be the operation of choice for marked congenital ptosis.

When the percentage of full corrections was compared for the two procedures, the results were essentially the same, being 39.7% for the internal and 39.8% for the external method. However, the conjunctival approach produced 60.2% and the skin route only 40.7% undercorrections. Therefore, the external was the better operation for marked ptosis. But since the external procedure produced 19.4% overcorrections and the internal none, it would seem that the latter was better in this respect. However, this is not a valid conclusion because many of these overcorrections could have been prevented by undercorrecting the ptosis the proper amount at operation.

Therefore, since the external method seemed easier to perform and gave a greater amount of correction and since the number of undercorrections was less, it would seem that resection of the levator through a skin

Fig. 36.—Overcorrection of 1 mm. Before operation (left), 21 days after (center), and nine months after (right). Levator action was 6 mm. Lid covered cornea 5 mm. before operation, 1 mm. at end of operation, and the same amount nine months later. Note marked improvement in lagophthalmos nine months after operation.

Fig. 37.—Undercorrection of 2 mm. associated with poor (2 mm.) levator action. Before operation (left) and 18 months later (right). Right upper lid was raised to limbus at operation, but 18 months later it had "fallen" to cover the cornea 4 mm. in primary position, even though levator was "good and thick" at operation. After operation esotropia with overaction of the right inferior oblique developed. Myectomy of right inferior oblique corrected the right hypertropia.

incision is the better operation for congenital ptosis.

The importance of accurately measuring the amount of levator action and of noting the position of the normal lid with respect to the cornea before operation is stressed because these two factors played a dominant role in determining the final result. For example, overcorrection and undercorrection could be prevented or reduced by undercorrecting the ptosis at operation when the levator action was good and overcorrecting it when the levator action was poor. By this formula the number of overcorrections and undercorrections was much reduced and the number of full corrections increased. Since only 5% of the secondary operations were undercorrected when the levator action was good, a second resection of the levator would appear to be the operation of choice in these patients, but since only 27.3% were fully corrected after a second resection when the levator action was poor, one should be prepared to use one of the other types of operations if the levator muscle is too frail to support the lid fully.

Overcorrection of 2 to 3 mm. was remedied by a simple tenotomy of the levator through the conjunctival surface in eight cases, with improvement in all.

The amount of preoperative levator action was a better guide to the final result than the gross appearance of the levator muscle

Fig. 38.—Poor result with poor levator action (3 mm. O. U.). Before operation (left), three months after (center), and one and one-half years after (right). Each upper lid could be raised to cover each cornea only 2 to 3 mm. at end of operation because each levator was "paper thin." Even though the right levator was thick and fibrous at the second operation and even though the lid covered the cornea 2 mm. at the end of operation, the lid "fell" to almost cover the pupil one year later. Thus, "good" levator tissue with poor levator action is not adequate to support a ptotic lid.

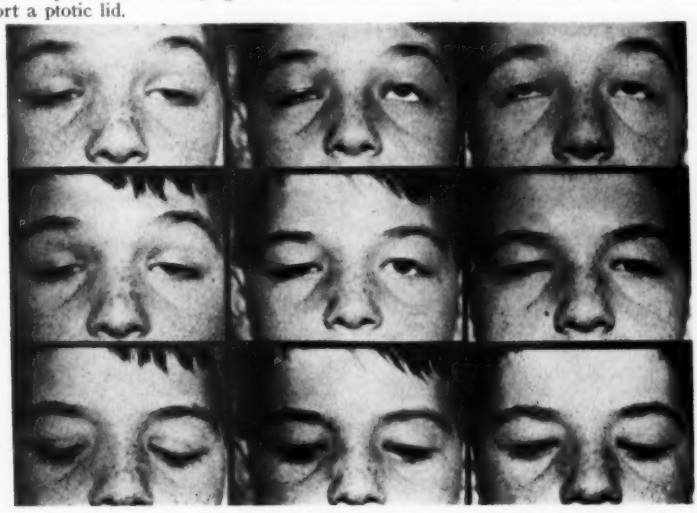


Fig. 39.—Paralysis of elevators of right eye with true ptosis and good (10 mm.) levator action. Before operation (left), after operation for hypertrophia (center), and after operation for ptosis (right). After operation to enhance the elevators and weaken the depressors of the right eye, the ptosis was worse. Resection of the levator raised the lid to cover cornea 4 mm. at end of operation and 2 mm. 11 months later. Redundant skin of right upper lid should be excised. Many striated muscle fibers in biopsy specimen.

Fig. 40.—Good result in congenital third nerve paralysis. Before operation (left and after operation (right). Levator action was only 3 mm. from eyes down to eyes up, but a marked pseudo von Graefe sign was present on adduction of left eye. At operation the left lateral rectus was receded behind the equator; the left superior oblique was tenectomized, and the left lid was lifted to cover the cornea 3 mm. at end of operation.

at operation. When the levator action was good, striated muscle fibers were nearly always found histologically in the biopsy specimen. Operation increased the amount of preoperative levator action an average of 2.2 mm. The best suture material for resection of the levator in children is 0000 plain absorbable surgical (gut) sutures, all chromic surgical material lasting too long.

Conclusions

1. The external method for resection of the levator was better than the internal operation in congenital ptosis because (*a*) it produced a greater amount of correction and (*b*) the operation was easier for the average surgeon.

2. The external method gave a greater amount of correction because (*a*) more levator tissue could be excised and (*b*) the levator was advanced on the tarsus.

3. A survey of 147 external operations showed that (*a*) final overcorrection was the rule in the presence of good levator

Fig. 41.—*A* and *B*, before operation; *C* and *D*, after operation. Same case as in Figure 40. Note overcorrection of ptosis in eyes right (*C*) and undercorrection in eyes left (*D*).

Figure 41

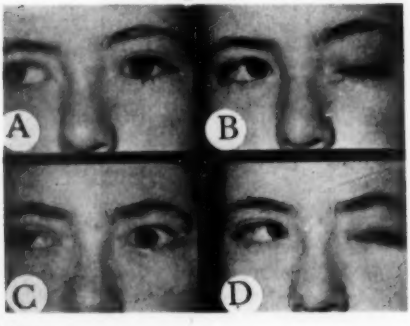
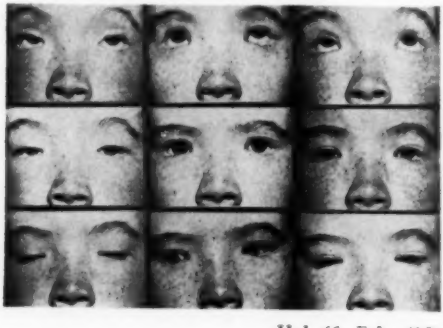


Fig. 42.—Good result in moderate blepharophimosis. Before operation (left), nine months after (center), and three and one-half years after (right). Levator action measured 8 mm. each eye before operation. Right upper lid was raised to limbus and the left to cover the cornea 1 to 2 mm. at end of operation. Note that the right upper lid was higher than the left nine months after operation but lower three years later.

Figure 42



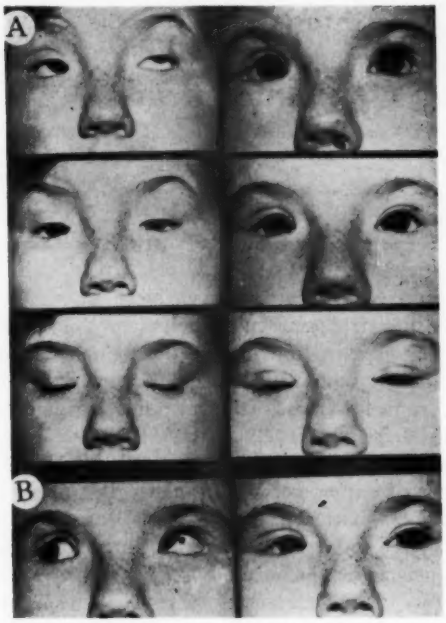


Fig. 43.—Good result in blepharophimosis with marked overaction of each inferior oblique muscle before operation. *A*, before operation (left) and seven months after (right). *B*, eyes right and eyes left. Note notch in right upper lid due to band-to-pulley and overaction of left inferior oblique *B* (left), overaction of right inferior oblique disappeared after operation because of an induced adhesion between the pulley and the lid, which prevented the upshoot of the right eye in adduction. Levator action was 7 to 8 mm. each eye. Lids covered corneas 3 mm. at end of operation. No striated muscle fibers in either biopsy specimen.

action unless the ptosis was undercorrected at the time of operation; (*b*) final undercorrection was the rule in the presence of poor levator action unless the ptosis was overcorrected at operation; (*c*) overcorrection of the ptosis on the operating table was impossible when the levator muscle was too thin to support the lid adequately, and (*d*) a second resection of the levator gave a high percentage of satisfactory results only when the levator action was good.

4. Full correction of the ptosis was obtained in over 70% of the (*a*) cases by the external operation whenever the ptosis was undercorrected on the table 2 or 3 mm. in the presence of 10 to 12 mm. of levator action; the ptosis was fully corrected and the levator action was 7 mm. in amount; (*c*) the ptosis was overcorrected 2 to 3 mm. and the levator function measured less than 4 mm.

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430 Union St.

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Chronic Progressive External Ophthalmoplegia

Report of a Case with Histopathologic Examination of External Eye Muscle and Skeletal Muscle

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In recent years several investigators have described the histologic findings made in the external eye muscles in biopsies or necropsies in cases of chronic progressive external ophthalmoplegia.[2,4,7,8,12,13] The authors cited agree that the changes are of the type usually seen in skeletal muscles in progressive muscular dystrophy, and they are of the opinion that chronic progressive external ophthalmoplegia is closely related to progressive muscular dystrophy and represents a particular type of this disease with preponderant or selective affection of the extrinsic eye muscles. Further support for this view is found in the concomitant occurrence of dystrophic changes in skeletal muscles in some cases.[4,7,8] The previously generally accepted opinion that progressive external ophthalmoplegia is primarily an affection of the nuclei of the eye muscle nerves appears to rest on insufficient evidence, as discussed by Kiloh and Nevin,[7] Schwarz and Liu,[13] and Adams, Denny-Brown, and Pearson.[1] The latter authors list the disease among the progressive muscular dystrophies.

This report presents an additional case in support of this view which is now gaining more and more ground.

Report of Case

History and Clinical Findings.—A female factory worker, aged 53, was admitted to the Ophthalmologic Clinic, Kristianstad, Sweden, in November, 1956.

None of her relatives were known to suffer from muscular, neurologic, or mental diseases, and no eye disease similar to that of the patient had occurred in the family. When treated by an ophthalmologist for chalazion in May, 1947, her oculomotor system was found to be intact. She had been in good health until her present illness started, in the beginning of 1950.

In October, 1950, she sought ophthalmologic advice because of drooping upper eyelids. This interferred with her vision so markedly that she had great difficulties in her work. Her ptosis had progressed slowly but without fluctuations for more than half a year. She had felt tired and complained of muscular weakness. She had not been aware of any restriction of her eye movements and had not noted diplopia. On ophthalmologic examination a pronounced bilateral ptosis and an almost complete external ophthalmoplegia, equal in both eyes, was found. There was no strabismus. The corneal sensibility appeared to be somewhat reduced. The pupils reacted well to light, and both ocular fundi were normal. After correction for myopia and astigmatism, her visual acuity was 0.9 and 0.1 in the right and left eye, respectively. The visual fields were normal.

Since 1950 and up to 1956 she has been repeatedly examined by ophthalmologists and internists, and on several occasions she has been admitted to internal medical departments. The patient's complaints during these years have varied from time to time: headache, sore throat, fluctuating pains in joints and muscles, muscular weakness, palpitations of the heart, dyspnea, tiredness, nervousness and periodic mental depression,

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vertigo on quick movements of the head, sleeplessness, and bad appetite. The muscular weakness has usually been more pronounced in the morning than in the evening. In 1952 tonsillectomy was performed because of chronic tonsillitis.

The results of repeated clinical examinations and the laboratory findings may be summarized as follows. She has an asthenic constitution. Her intelligence has been estimated to be fair. No additional ocular symptoms have appeared. The other cranial nerves and the peripheral nervous system have shown no abnormalities. No objective signs of weakness of muscles of the trunk or limbs have been found. During the period of tonsillitis in 1952, she presented moderate clinical symptoms of rheumatoid arthritis in knee and ankle joints.

X-ray examinations of lungs and heart and several electrocardiograms have been normal, as have routine laboratory tests of blood and urine and cerebrospinal fluid.

In 1953 repeated analyses showed urinary excretion of creatine to be 390 to 780 mg. in 25 hours and of creatinine, 750 to 900 mg., on one occasion 1800 mg. Intramuscular injections of neostigmine (Prostigmin) did not influence the ptosis or motility of her eyes. Her body weight has increased from 42.5 kg. in 1950 to 54 kg. in 1956. Her height is 157 cm.

Her ailments have been diagnosed as complete bilateral external ophthalmoplegia, rheumatoid arthritis and chronic tonsillitis, neurosis, and postencephalitic state (based on the assumption that an encephalitis earlier in her life might have resulted in a degeneration of the oculomotor nuclei). She has been treated in periods with tonics, sedatives, hypnotics, and analgetics and furthermore with vitamins B and E and ascorbic acid (Vitamin C), often in great doses, without any effect.

On examination in November, 1956, the following findings were made: She kept her head tilted backward, and her forehead was markedly and constantly wrinkled, with the eyebrows raised above the supraorbital margins; good strength in the frontalis muscle and the corrugator supercilii; bilateral ptosis. When she was looking straight ahead (Fig. 1*A*), about three-quarters of the right and two-thirds of the left pupil were covered. Both eyes could be well closed with no appreciable weakness of the

Fig. 1.—Unretouched photographs showing the practically complete immobility of the eyes. *A*, patient looks straight ahead. *B*, no Bell's phenomenon on attempt to close the eyes. *C*, patient attempts to look to the right and *D*, to look downward.

orbicularis oculi muscles. The eyeballs were in the primary position, and their movements were restricted to scarcely visible excursions in all directions (Fig. 1*C* and *D*), voluntary and reflexive. There was no converging power, and Bell's phenomenon was absent (Fig. 1*B*). The sensibility of both corneae seemed to be somewhat reduced. The patient, however, declared that she could feel the slightest touch of cotton wool on the cornea, but the blink reflexes were not adequate. The pupils were circular and equal in size. Their reactions to light were within normal limits, though possibly somewhat sluggish. There was no cataract, and both ocular fundi were normal. By manual elevation of both upper lids there was blurred vision and inconstant diplopia within 60 to 70 cm. There was no diplopia at distance. Her face was expressionless, her neck, thin. The muscles of the neck, trunk, and legs appeared normal on physical examination. However, the patient complained of considerable weakness in her neck and legs. Only by great effort could she elevate her head from the pillow, and each leg could barely be raised above the other knee. There was thus a lack of proportion between the patient's own feeling of strength and the physical findings.

At this time there was no creatine in the urine. The excretion of creatinine was 460 mg. in 24 hours.

In order to obtain information as to the character of the external ophthalmoplegia, the right eye was locally anesthetized with tetracaine (Pontocaine) and the conjunctiva bulbi was grasped with a forceps. The eye could then be turned in all directions without abnormal muscular resistance, showing that there was no spastic paralysis. Biopsy specimens were then taken from the right external rectus and the right sternocleidomastoid muscle for histologic examination.

The patient was again seen in the Ophthalmologic Clinic in December, 1957. Her general condition had deteriorated somewhat, but the physical findings were as those reported above. A psychiatric examination showed no intellectual inferiority but an obvious bradyphrenia revealing itself by her slow comprehension and speech. There were no obvious signs of amnesia or aphasia. Her face was almost motionless. The psychiatric diagnosis was "a marked pathological syndrome of organic type." Now the laboratory examination showed the amounts of creatine and creatinine in the urine to be 160 and 740 mg., respectively, in 24 hours.

The patient's opinion on her condition at this time was that the sudden death of one of her sisters two months previously had caused a pronounced mental depression.

The psychiatric symptoms progressed rapidly. A few days later the patient was sitting immobile, but she could shake hands, seemingly with great effort. She was unable to talk, but she could masticate and swallow. There was incontinence of bladder and bowels. She was admitted to St. Lars Hospital for Mental Diseases, Lund.

Histologic Examination.—The biopsy specimens were kept for two hours in gauze moistened with Ringer's solution and then transferred to 8% formalin. After fixation the blocks were embedded in paraffin. Some serial sections, 15μ thick, were made in a plane approximately transversely to the muscle fibers; others were made in their longitudinal direction. Most sections were stained with hematoxylin and eosin, or the Van Gieson stain, while some were treated with the Mallory stain or impregnated with silver according to the Bielschowsky-Maresh method for reticular fibers.

Right External Rectus Muscle: There is a considerable increase in connective tissue. Certain regions of the biopsy specimen consist exclusively of dense bundles of collagenous fibers; in other places scattered muscle fibers are seen embedded in connective tissue. Still other regions contain a fair number of muscle fibers, but even here collagenous fibers, usually of a finer caliber, are present in increased numbers between the individual muscle fibers (Fig. 2*A* and *B*). Only rarely a few muscle fibers are

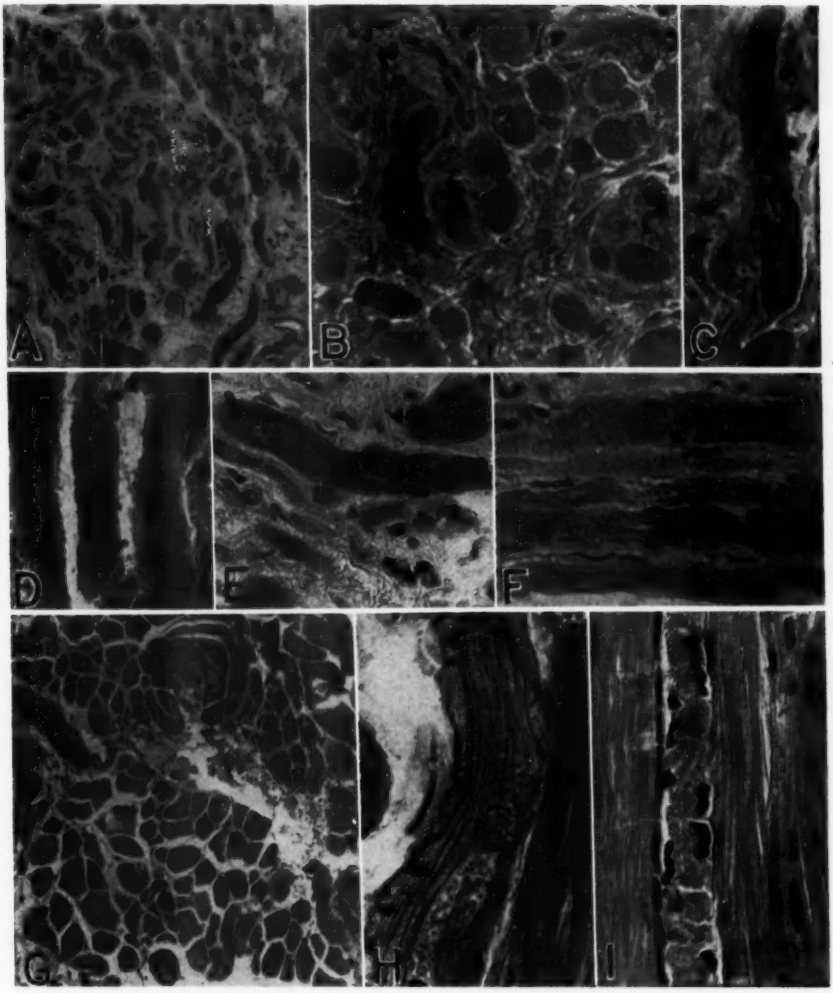

Fig. 2.—Unretouched photomicrographs from the external rectus muscle (*A-F*) and from the sternocleidomastoid muscle (*G-I*). *B* and *E* are from Van Gieson-stained sections; the others are from sections stained with hematoxylin and eosin. *A*, transverse section, external rectus muscle. Atrophy of muscle fibers, with increase of connective tissue. *B*, transverse section, external rectus muscle. Increase of connective tissue between the individual muscle fibers which have varying diameters. *C-F*, "degenerating" fibers in external rectus muscle, showing granular sarcoplasm. In *C* a row of subsarcolemmal nuclei; in *D* a cluster of pyknotic nuclei, in *E* rounded abnormal nuclei. *G*, transverse section, sternocleidomastoid muscle. Fibers in different stages of atrophy irregularly intermingled. *H*, muscle fiber from the sternocleidomastoid muscle showing some preserved myofibrils in a granular sarcoplasm. *I*, from the same muscle as Figure *H*. Fiber showing hyperchromatic nuclei; normal fibers on both sides. *A* and *G*, reduced about 10% from mag. × 120; all others reduced about 10% from mag. × 220.

seen lying closely together, not separated by collagenous fibers.

The diameters of the muscle fibers vary between 7μ and 30μ. The majority have diameters of 10μ to 20μ. There is no regular arrangement of fibers of particular diameters in groups. When seen in longitudinal section, about half the number of fibers

show preserved myofibrils with distinct cross striations. Even some extremely atrophic fibers have retained their cross striation, while, on the other hand, fibers with approximately normal caliber may show "degenerative" changes. The sarcoplasm has a granular appearance (Fig. 2*D-F*). In some of these fibers small vacuoles occur; in others some preserved myofibrils may be seen in the granular mass. These preserved myofibrils are most commonly situated underneath the sarcolemma.

In the muscle fibers having a normal appearance with preserved cross striations, the nuclei usually appear normal and have a distinct nucleolus. In fibers showing "degenerative" changes as described above, such nuclei are rare. Most of their nuclei are pyknotic, dark, and homogeneous (Fig. 2*C-D*) and may have irregular outlines. In some fibers of this type pyknotic nuclei are arranged in rows of four to eight underneath the sarcolemma (Fig. 2*C*), or they may appear clumped together (Fig. 2*D*). Other nuclei in the fibers affected with "degenerative" changes appear larger and rounder than the normal ones and usually lack a nucleolus and a network of chromatin (Fig. 2*E*).

Right Sternocleidomastoid Muscle: There is no convincing increase of connective tissue between the primary muscle bundles. However, in a few of them strands of collagenous fibers extend in between the muscle fibers, surrounding the individual fibers on all sides. The majority of the muscle fibers appear to have a normal structure, but their diameters vary between 8μ and 45μ. Most of them are approximately 30μ thick and thus are certainly atrophic. However, muscle fibers in the same degree of atrophy are not collected in groups, but fibers in different stages of atrophy are irregularly intermingled (Fig. 2*G*). In longitudinal sections the cross striations are distinct in most fibers (Fig. 2*I*). In a few the cross striations are absent and the sarcoplasm has a granular appearance; in others it presents what Greenfield et al.[5] call a "floccular change." As in the external rectus muscle, some fibers still have some preserved myofibrils in an otherwise granular sarcoplasm (Fig. 2*H*). In most of the muscle fibers the nuclei show no abnormal features, but in some fibers long chains of nuclei are found under the sarcolemma. These nuclei may be somewhat more densely stained than the normal nuclei and have an increased basophilia (Fig. 2*I*). Particularly in the most atrophic fibers, chains of darkly staining pyknotic nuclei are frequently seen. Occasionally such cells are collected into dense clusters as in the external rectus muscle (see Fig. 2*D*).

Some bundles of nerve fibers which are found in the section appear normal, as far as can be judged on the basis of the staining methods employed. The same is the case with a muscle spindle which is included in the biopsy specimen. No pathological changes are found in the vessels.

Comment

The case history and the clinical findings in our case make clear that the diagnosis of chronic progressive external ophthalmoplegia is justified. (For a recent review of the clinical aspects see, for example, Kiloh and Nevin.[7]) From a clinical point of view, the present case shows nothing particularly striking. Several authors emphasize the importance of heredity in the pathogenesis of this disease. No evidence that hereditary factors were involved could be found in our case, but obviously the absence of the disease among the few relatives of the patient does not permit any conclusions.

It may be asked whether there is any relation between the ophthalmoplegia in our case and the signs of "nervousness" and psychic deterioration exhibited by the patient, particularly during the last year. In spite of the conclusion by the psychiatrist that she presented "a marked pathological syndrome of organic type," there were no neurologic signs pointing to an affection of the central nervous system. It appears most likely that her nervous and psychic dis-

orders, of whatever nature they may be, are not directly related to her ophthalmoplegia. It may be noticed, however, that there is some similarity between our patient and McAuley's Case 2 in this respect.[8]

It is generally conceded that creatinuria is common in all kinds of diseases affecting the general musculature and that it is particularly marked in muscular dystrophies.[9-11,14] Its occurrence in our case on some occasions is, therefore, worthy of notice. However, the creatinuria was rather moderate, being 7 to 15 mg. per kilogram of body weight in 24 hours in 1953 and about 5 in 1957. Since some normal women exhibit slight creatinuria either constantly or at intervals,[10] as do children,[10,14] much weight cannot be attributed to the creatinuria in our case. Since there appears to be a relation between the amount of creatine in the urine and the degree of muscular wasting,[9,10] one would scarcely expect large quantities of creatine to be excreted in progressive external ophthalmoplegia, even if this is a disorder belonging to the muscular dystrophies. The values of the creatinine coefficient (ratio of milligrams of creatinine in 24-hour urine to body weight in kilograms) in our case (14 to 17, 9, and 15 on different occasions) are also within the normal range for women.[10,11] (Only once it was found to be 34.) The analyses of urinary excretion of creatine and creatinine in our case thus do not give any information with regard to the nature of the disease.

Of major interest in the present case are the results of the histologic examination. The sections from the external rectus muscle showed several histologic features which are regularly seen in muscles in clinically verified cases of progressive muscular dystrophy,[1,6,15] such as a marked increase in connective tissue with infiltration of collagenous fibers even between the muscle fibers of primary muscle bundles. Furthermore, the presence of fibers in practically every degree of atrophy and the absence of grouping of fibers in the same stage of atrophy is characteristic, in contrast to the pictures usually seen in muscular atrophies due to lesions of peripheral motor neurons. Here, commonly, fibers affected to the same degree are lying collected in groups of 8 to 50 fibers.[1,16] Finally, the "degenerative" changes in the sarcoplasm of some fibers (granulation, loss of cross striation) are changes almost constantly found in dystrophic affections but lacking or extremely rare in neurogenic muscular atrophies. Long rows of subsarcolemmal chiefly pyknotic nuclei, found in the external rectus muscle in this case, however, are more commonly seen in neurogenic atrophies than in dystrophic muscles. In the latter such nuclear chains are usually centrally placed.[17] Yet, this feature alone is not sufficient to invalidate the conclusion that the changes found in the external rectus muscle in our case are to be considered as dystrophic, since the presence of the other changes carries more weight.

For an evaluation of the relation between chronic progressive external ophthalmoplegia and the progressive muscular dystrophies, it is of relevance to know whether dystrophic changes are present in skeletal muscles as well in cases of progressive external ophthalmoplegia. It is generally held that clinical signs of affection of skeletal muscles are usually absent in this disease, and according to Kiloh and Nevin,[7] affection of the external eye muscles in the well-known types of progressive muscular dystrophy is extremely uncommon. Yet, some cases with combined involvement of skeletal muscles and external eye muscles have been reported (for a review of the literature, see Kiloh and Nevin[7]). Since it is possible that a muscle may be affected histologically without presenting definite clinical wasting or paresis, biopsies of skeletal muscles in cases of progressive external ophthalmoplegia may give information of value. A few cases where such biopsies have been made have been reported. Thus Kiloh and Nevin,[7] in one of their cases, found pathologic changes of the dystrophic type in the orbicularis oculi and the

lateral vastus muscle; in another case, in the deltoid muscle, and in a third, in the orbicularis oculi muscle. McAuley [8] studied the pectineus in one case, the deltoid in another. In all of these cases the changes were far less pronounced in the skeletal muscle studied than in the external eye muscles. This is also true in our case. However, the findings made in the sternocleidomastoid are strongly suggestive that the pathologic process is of the dystrophic type. Thus the absence of grouping of fibers in the same stage of atrophy, the infiltration of collagenous fibers between muscle fibers in the primary muscle bundles, and the slight but unequivocal "degenerative" changes in the sarcoplasm of some of the fibers are findings commonly made in the affected muscles in progressive muscular dystrophies. The similarity in the pathologic changes in external eye muscles and in skeletal muscle in our own and some of the previously reported cases furnishes evidence in favor of the opinion that chronic progressive external ophthalmoplegia is closely related to the chronic progressive muscular dystrophies.

The infrequent simultaneous clinical occurrence of muscular dystrophy of the usual types and chronic progressive external ophthalmoplegia may seem to contradict the opinion that there is any close relation between them. However, as is well known, the progressive muscular dystrophies may be subdivided into various forms which differ with regard to their preferential localization, time on onset, course, heredity, and other features. The reasons for these variations are unknown, but they are compatible with the view that chronic external progressive ophthalmoplegia may be a particular form within the larger group of muscular dystrophies. Much more pathological material will have to be examined before it can be decided whether the histologic changes in the affected muscles may give any clue in this respect. The occurrence of long rows of pyknotic subsarcolemmal nuclei in the external rectus muscle and the sternocleidomastoid in our case may be an indication that there are minor differences between the histological changes in this form of myopathy and those affecting primarily the skeletal muscles, and it is interesting to note that similar chains of subsarcolemmal nuclei were found in external eye muscles in some of the cases described by others.[2,8] Too much importance should, however, not be attributed to this isolated finding. Greenfield and his collaborators [5] have recently emphasized that pathologic changes in the muscles specific to a particular disease process scarcely exist, a statement to which one of us (A. B.), having examined a rather large number of such biopsy specimens, will subscribe. Nevertheless, certain features in the pathology may be sufficiently characteristic to merit attention in differential diagnosis. An illustrating example is furnished by progressive peroneal muscular atrophy (Charcot-Marie-Tooth disease). In spite of a number of histologic changes in the muscles which indicate that this disease is primarily an affection of the lower motor neurons, "degenerative" changes in the muscle fibers are rather prominent,[3] in contrast to, for example, amyotrophic lateral sclerosis.[1,16] It appears, therefore, that it would be of importance in future studies of biopsy specimens from external eye muscles to pay attention to the possible occurrence of pathologic features which may distinguish chronic progressive external ophthalmoplegia from other forms of muscular dystrophies.

The question of the classification of the disease under consideration may, however, not be as simple as one might believe from the few reports published on its pathology. It should be realized that the fact that dystrophic changes have been found in several cases of chronic progressive external ophthalmoplegia does not permit a definite statement that this disease, as classified on the basis of clinical criteria, is always a form of progressive muscular dystrophy. One of us (A. B.) has recently examined biopsy

specimens from two cases which were clinically typical, but, in spite of this, no pathologic changes could be found either in eye muscles or in biopsy specimens from the deltoid muscle.

Summary

A case of chronic progressive external ophthalmoplegia in a middle-aged woman is described. Her symptoms started at the age of 47, and in the course of a few years a complete external ophthalmoplegia developed.

The excretion of creatine and creatinine in the urine showed no significant changes.

Biopsy of the right external rectus muscle showed histologic changes similar to those found in cases of muscular dystrophy: increase of connective tissue, even within the primary muscle bundles; atrophy of muscle fibers without grouping of fibers in the same stage of atrophy; granular "degeneration" of the sarcoplasm in some fibers with loss of myofibrils, and changes in the nuclei of the muscle fibers. Biopsy of the sternocleidomastoid muscle showed similar but less marked changes of the same type.

The histologic findings are in agreement with the view that progressive chronic external ophthalmoplegia may be a particular form of muscular dystrophy. Some features of the histologic changes are discussed from this point of view. It is emphasized that it would be premature to conclude that all cases diagnosed clinically as progressive chronic external ophthalmoplegia are of the myopathic type.

Lasarettsläkare Herman Grönvall, M.D., Head of the Ophthalmologic Clinic, Kristianstad, Sweden, gave permission to use the clinic's records concerning the patient.

Anatomical Institute, University of Oslo, Karl Johans gt. 47 (Dr. Brodal).

Addendum

After the present paper was completed, Kirschbaum and Holland (*Neurology* 8: 304-306, 1958) published a report of a case of chronic progressive external ophthalmoplegia. The histologic changes, which are very briefly described, are interpreted as being of the dystrophic type.

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Amaurosis Congenita (Leber)

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Introduction

In 1869 Leber,[1] at the time consulting ophthalmologist of the Ilvesheim Institute for the Blind, described a type of blindness occurring at birth or soon after. In some of the affected children residual vision was found. In most of the cases a marked nystagmus was present and photophobia was recorded in spite of the extremely poor visual function. Even in the few cases in which the visual function was less defective, it was obvious that the pupil reactions were slow and incomplete. In some of the cases of complete blindness, however, a rudimentary pupil reaction was observed.

In those cases having some residual vision, the visual fields were in most instances not markedly contracted. In some of the less-affected children a marked degree of night blindness was recorded. In the first months of life it was not possible to observe essential alterations in the fundus oculi. In a later phase minor pigmentations occurred, in a few cases changing toward bone-corpuscle-like pigmentation. In those cases also a narrowing of the retinal vessels and beginning optic atrophy could be observed. In a minority of cases the fundus stayed normal, in spite of the severely impaired visual function. In the majority of cases a diffuse atypical pigmentation occurred. In some of the older cases complicated cataracts were found.

On the basis of the ophthalmoscopic picture and the visual function, Leber classified this affection as belonging to the tapetoretinal degenerations, *Tapetoretinale Degeneration mit Amblyopie;* he suggested the name amaurosis congenita. Leber also stressed the high incidence of hereditary factors: consanguinity of the normal parents in 24.1% and blind siblings in 20.7%.

Waardenburg [2] in 1956 presented some 12 cases which might well belong to the above-described disease. However, he stressed in particular the high incidence of keratoglobus, a symptom not mentioned by Leber. Waardenburg discussed the possibility of an agenesis or dysgenesis neuroepithelialis retinae as a cause of this connatal affection. In the same year, one of us [3] discussed the value of electroretinography in cases of doubtful diagnosis in blind or partially sighted children.

In 16 cases of the condition under discussion a diagnosis of dysfunction of the retina was made, based upon the absence of the ERG, although in some of the cases a highly reduced response of probably photopic nature could be recorded.

In 1957 Alström and Olson [4] published an extensive study called heredoretinopathia congenitalis monohybrida recessiva autosomalis, describing a large number of cases of an affection which might well fit in with Leber's description. Cataract and keratoconus, however, were found in a substantial number of cases. Genetically, this Swedish study is highly important in establishing beyond doubt the recessive autosomal character of this condition. We had the opportunity of examining some of the chil-

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Eye Clinic, Rotterdam (Dr. Henkes); Human Geneticist of the Netherlands Institute for Preventive Medicine, Leyden (Dr. van den Bosch).

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dren described.* We are convinced that the affection described by Alström and Olson is the same as that reported by Waardenburg.

Franceschetti and Dieterlé [5] also described some cases of Leber's amaurosis congenita, stressing the value of electroretinography in the diagnosis.

Present Study

The present material consists of 227 cases of amaurosis congenita, of which 114 are adults and 113 are children. Of the latter, 109 are blind and only 4 are partially sighted (the definition of blindness used in this investigation is a vision of 1/10 or less; vision of the partially sighted, up to 1/4). The material was collected in the course of an investigation into the causes of blindness in the Netherlands by one of us (J. S. K.). The number of blind children registered so far seems to be fairly complete; it is considered to be approximately 600. The percentage of this disease in the general population of known blind persons (adults and children together, approximately 6000) is 3.8%, whereas in children we have calculated an incidence of as much as 18%! Alström and Olson found an almost equally high incidence in Sweden.

The data of the 227 cases under discussion were submitted to us by a large group of Dutch ophthalmologists. Owing to the high incidence of the affection it should be reasonable to assume that the condition is familiar to the majority of ophthalmologists. However, this is not the case. Various diagnosis were made; the most frequently found were the following: (1) connatal amaurosis of unknown origin (probably centrally located, e. g., cerebral hemorrhage during delivery); (2) diffuse chorioretinitis (congenital syphilis?); (3) atypical tapetoretinal degeneration, e. g., retinitis pigmentosa sine pigmento, and (4) connatal optic atrophy.

* Dr. Alström and Dr. Olson arranged for personal examination of a number of their cases at Tomteboda Institute for the Blind, Stockholm.

It seemed important to us to study the affection in its earlier stages. Therefore we confined our investigation to the affected children.

Of the 113 cases, 56 were examined in detail by ourselves, with electroretinographic examination. In the following pages data will be given of these 56 cases. The distribution of their ages at the time of our first examination was as follows: from 1 to 5 years of age, 3 cases; from 6 to 10 years, 18 cases, and from 11 to 18 years, 35 cases.

The following diagnoses were made by the referring ophthalmologist:

Diagnosis	Cases, No.
1. Tapetoretinal degeneration	30
2. Blindness or amblyopia of central origin	13
3. Connatal optic atrophy	4
4. Achromatopsia	3
5. Anomalies of optic nerve	2
6. Congenital cataract	1
7. Albinism or choroideremia	2
8. Amaurosis congenita Leber	1

Symptoms

Obligatory symptoms of amaurosis congenita (Leber) are (1) connatal amaurosis or highly impaired vision, (2) a fundus picture showing a marked discrepancy between this and the visual function, (3) a recessive heredity, and (4) an absent ERG or at least a markedly reduced electrical activity of the retina.

In the majority of cases nystagmus or nystagmoid eye movements may be recorded.

Facultative symptoms are (1) photophobia, (2) cataract, and (3) keratoglobus or keratoconus. The latter two conditions seem to develop in a later phase of the affection.

Generally speaking, the visual fields—if recordable—do not show marked constriction, in contrast with the constriction found in most cases of primary pigmentary degeneration.

Each of the symptoms mentioned above needs a discussion in some detail.

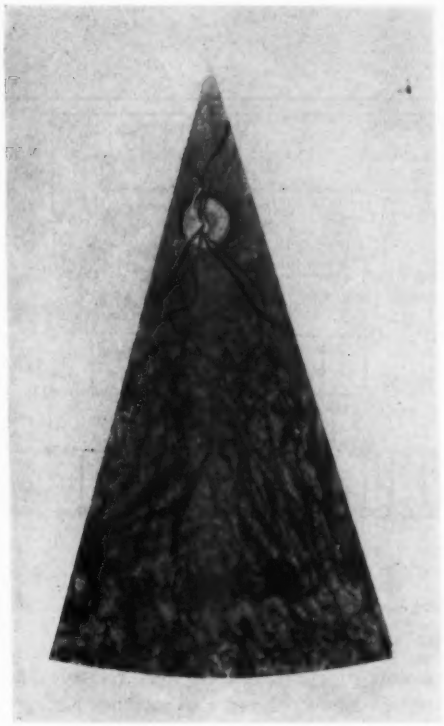

Fig. 1 (Case 1).—Fundus picture of a typical case of amaurosis congenita (Leber). Only minor alterations are visible: "thinning" of the peripheral retina and diffuse pigment dispersion. Doubtful optic atrophy.

Visual Acuity

Among the 56 children, vision was zero in 4 cases. There was vision up to hand movements at 1 meter in 22 cases; vision up to finger counting at 1 meter in 11 cases; vision up to 1/10 in 10 cases, and vision over 1/10 in the better eye in 3 cases. In 6 cases it was virtually impossible to record the visual acuity, owing to the age of the child and the existence of marked photophobia.

Fundus Picture

The ophthalmoscopic picture is rather polymorphous. In the young patient an almost normal appearance is common (Fig. 1). During life this appearance may change considerably. Commonest is a dingy, disorderly appearance of the fundus with—in some of the cases, especially the older ones—in a later phase atypical pigmentation and depigmentation, especially in the periphery of the fundus.

Incidentally, a pepper-and-salt fundus is diagnosed. In many a case, however, an albinotic appearance is notable. A marked alteration of the macular region also may be recorded. In a large number of cases some narrowing of the retinal vessels and a slight optic atrophy is mentioned. Of the 56 cases observed, the fundus picture was described as follows:

Fundus Appearance	Cases, No.
1. Normal	5
2. Atypical pigmentation and depigmentation	39
3. Typical, bone-corpuscle-like pigmentations	8
4. Markedly altered macular region	16
5. Attenuation of the retinal vessels	35
6. Some optic atrophy	39
7. Pseudopapillitis and other anomalies	12

Recessive Heredity

There were 42 of the 56 children under discussion who were free from major neurologic and/or psychiatric defects. Intentionally, in the study of hereditary factors we eliminated mentally defective patients in order to make a comparison possible between our data and those of Alström and Olson (Alström and Olson eliminated the physically and mentally defective probands from their material). Twenty-two of these forty-two children were from families showing the disease. Of these, we found in 1 family four connatally blind children; in 2 families, three connatally blind children; in two families, two connatally blind children, and in 11 families, more than one connatal blind child. However, in each family only one child was examined personally, the others being examined by other ophthalmologists, who submitted their data of these affected children to us.

The recessive autosomal character of amaurosis congenita (Leber) is made clear by the study of the first pedigree chart of the Netherlands (Fig. 2). In this chart

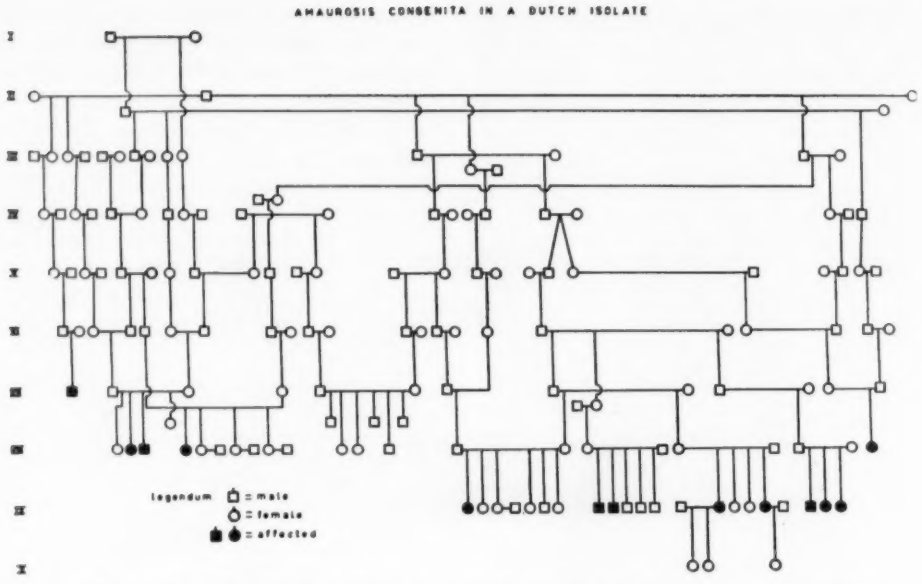

Fig. 2.—Pedigree chart of a family in a Dutch isolate, including 13 cases of amaurosis congenita (Leber).

13 cases have been included, most of them still living on the isle of Urk.

The demographic history of the population of this old isolate provides the student of population genetics with an ideal object of investigation. In 1637 only 151 of the 300 inhabitants survived the plague. As most marriages were endogamous up till 1941—when the island became part of the mainland, owing to reclamation of the Zuyderzee—the present population of about 4000 can be regarded as the progeny of at most 75 marriages in the 17th century. This means that the mean coefficient of inbreeding in this population must be extremely high. Therefore, many members of the population have common ancestors, from which they could have inherited a particular gene originating in one of these progenitors. Recessive genes for abnormal traits can act only in homozygous persons. As the number of common ancestors increases so does the probability of two recessives combining to form one abnormal homozygous person. For these reasons, it was not surprising to find the following data: (*a*) The parents of our probands were related; (*b*) the affection occurred also in other siblings, and (*c*) all these siblings proved to have one or more common ancestors. Furthermore, we were able to prove that: (*d*) None of the parents of the affected persons were affected themselves; (*e*) both males and females were about equally affected; (*f*) most of the parents were either related to each other or related to parents of other affected persons; (*g*) the ratio of affected to not affected sibs did not deviate significantly from the expectation in case a recessive gene was involved.

From the above, it seems to be justified to assume that amaurosis congenita in this isolate is the phenotypical expression of one or more autosomal recessive genes.

Electroretinogram

The series of 56 children under discussion was examined electroretinographically. Single-flash ERG's and flicker ERG's were employed according to the method published by one of us (Henkes[6]). Using the "usual" amplification of 500μv. per centi-

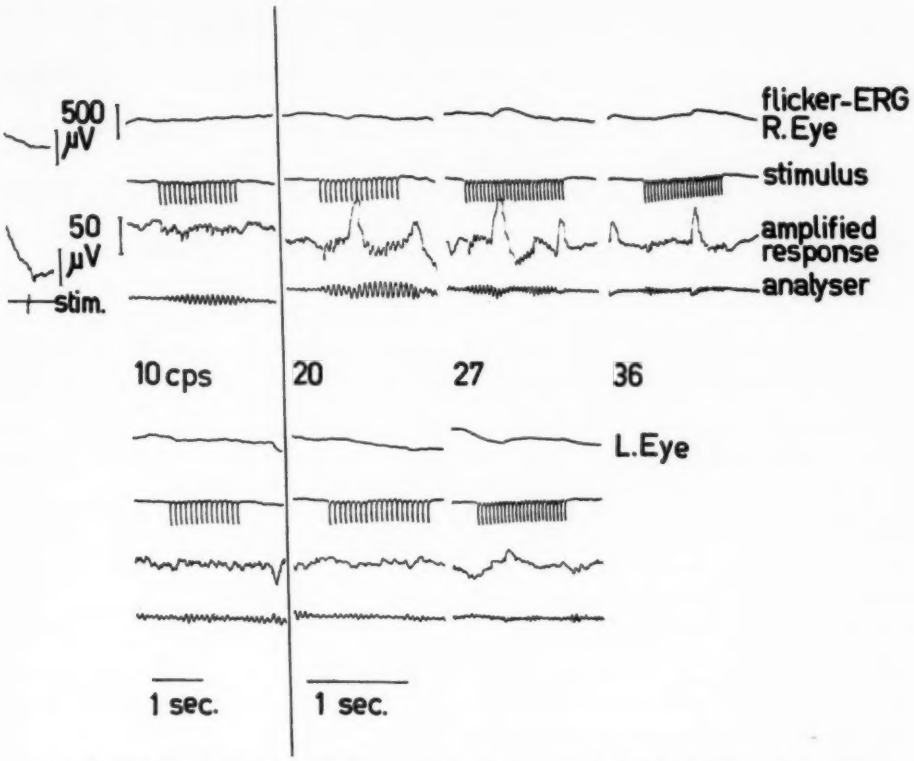

Fig. 3.—The ERG is a typical case of amaurosis congenita (Leber). Upper left, absent electrical response. However, the right eye shows a distinct negative response when the usual amplification is increased 10 times. Selective amplification, using frequency analyzer, demonstrates clear responses in the right eye up to 36 flashes per second. The left eye does not produce any response following either a single flash or flickering light. Intensity used: 6500 lumens; xenon-filled tube. Time constants: single-flash ERG, 1 second; flicker ERG, 0.1 second.

meter and Karpe's technique, only in two eyes could a clear scotopic response be recorded. An increase in stimulus intensity and at the same time the use of a method of selective amplification of the flickering response (see Henkes, van der Tweel, and van der Gon [6,7]), however, revealed a definite response in 42 of the 110 eyes, thus reducing the number of eyes with an absent ERG to 68. (The commonly used expression "extinguished" ERG [Karpe] is in our opinion misleading in these cases, as it suggests the presence of an electrical response beforehand, an assumption as yet to be proven.) The ERG's found in this way are very probably of photopic nature, as they could be demonstrated only by using a high gain of the recording apparatus and very high intensities of the light stimuli. They show a predominantly negative character, and the critical frequency of flicker fusion lies well within the photopic range.

In Figure 3 a so-called absent ERG is given in a case of amaurosis congenita (Case 1). With use of recording conditions routinely in use, the ERG is absent, both in the single-flash and in the flicker ERG (upper tracings), although the stimulus intensity is very high. (xenon-filled stroboscope tube, with an intensity comparable to 6500 lumens). However, an increase in amplification up to 50µv. per centimeter shows a small negative response in the single-flash ERG of the right eye.

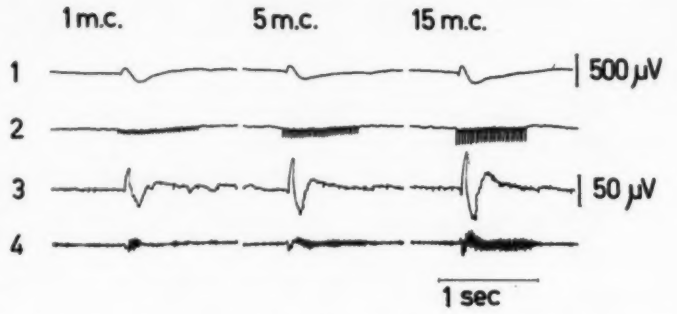

Fig. 4.—Determination of the critical intensity of flicker fusion (CIF) at 39 flashes per second. Tracing *1* and Tracing *3*, flicker ERG with different amplification and different time constants (Channel *1*, 1 second; Channel *3*, 0.1 second). Recording of stimulus in Channel *2*. Resonance channel (No. *4*) gives clear response at 5 lumens, no response at 1 lumen. CIF, 1 lumen.

In the amplified flicker ERG of this right eye the response is present at least up to 36 flashes per second, being well within the photopic range. The left eye does not produce a response either in the single-flash or in the flicker ERG. In the right eye flicker fusion was reached at 39 flashes per second when the maximum available light intensity of 6500 lumens was used. In most normal cases, for comparison, the critical frequency of flicker fusion is 39 flashes per second at an intensity not exceeding 5 lumens (or, to say it differently, the critical intensity of flicker fusion (CIF) is 5 lumens or less). It is clear that in this particular case the response of the cone system is very defective. For comparison, the determination of the CIF in a normal person at 39 flashes per second is given in Figure 4. With use of the method of the selective amplification of the flicker ERG, a resonance is clearly visible in the analyzer channel (No. 4) at an intensity of 5 lumens, whereas flicker responses cannot be seen in the normal or in the amplified flicker ERG. The CIF in this normal case is thus 1 lumen at 39 cps.

In one child only we did find a scotopic response under the "usual" recording conditions. Figure 5 gives the electroretinographic data in this case (Case 2), in which a b-potential was found of 51μv. in the right eye and of 73μv. in the left eye (stimulus intensity, 400 lumens). A rudimentary photopic response at 43 flashes per second could be recorded as well, using the selectively amplified flicker-response and a stimulus intensity of 5000 lumens.

The absence of an electrical response using the "normal" recording conditions in such a high percentage of the cases (in the present material in 110 of 112 eyes) may well be considered as a compulsory symptom of amaurosis congenita.

Karpe [8] is of the same conviction, although he was able to record subnormal responses also in some of the cases described by Alström and Olson.

The highly impaired electrical response indicates that the origin of the affection must be located within the retina, despite the fact that Winkelman [9] found, histologically, all retinal layers to be intact. In discussing Winkelman's report, Waardenburg was certainly correct in pointing out that a histological examination is unable to distinguish between normal and pathological functioning of the retina.

Other Symptoms

Nystagmus was present in 35 of the 56 children examined. Marked photophobia was recorded only in two children. As men-

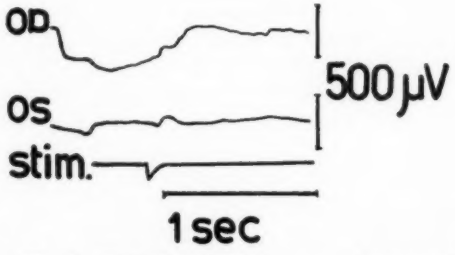

Fig. 5.—Single-flash ERG in a case of amaurosis congenita, showing scotopic responses of 51μv. and 73μv., respectively, for right and left eyes. Stimulus intensity, 400 lumens. Time constant, 1 second.

tioned above, cataracts were found only in a few eyes. This is due to the fact that cataract (as well as keratoglobus) usually develops at a later stage of the affection. We observed 15 eyes with cataracts and only 2 cases of keratoglobus. Obviously our findings differ markedly in this respect from those given by Alström and Olson, because they have studied older persons. The two cases of keratoglobus were found in the group of children 11 years of age or older at the time of the first examination. Of 15 eyes with cataract, 11 were found in this same age group.

Report of Typical Cases

CASE 1.—A 13-year-old girl has been blind since birth. A sister is equally affected. There is no consanguinity of the parents. Visual acuity: light projection positive. Nystagmus. Ophthalmoscopy reveals only minor alterations (Fig. 1). The retinas are "thin," especially in the periphery. Slight pigment dispersion is present all over the fundus, more marked in the periphery. The retinal vessels seem to be slightly contracted; the optic discs show a doubtful atrophy. If this girl had had normal visual function, one would have certainly been inclined to consider the fundus only as slightly abnormal, though without significance. The ERG is absent, at least under recording conditions used routinely (Fig. 3). Selective amplification reveals, however, a rudimentary response of photopic nature, at least in the right eye.

CASE 2.—A 14-year-old girl has been blind since birth. As far as can be established, this girl is the only one affected in the family. There is no consanguinity of the parents. Visual acuity: right eye, hand movements seen at 1 meter; left eye, fingers counted at 1 meter. Nystagmus. Ophthalmoscopy: diffuse pigmentation of the fundus oculi; slight atrophy of the optic discs. Diagnosis made at the age of 5: connatal optic atrophy with diffuse atrophy of the retina. The ERG shows a subnormal b-wave (Fig. 5) and a rudimentary photopic response in the amplified flicker ERG in both eyes.

Comment

No doubt the material presented is still incomplete. Intentionally we have presented only cases of amaurosis congenita found in children. In adults the fundus picture becomes less specific: The minor alterations of the fundus found in the majority of cases under the age of 18 years show a tendency toward increased pigmentation and local atrophic alterations. It may be difficult to differentiate between amaurosis congenita (Leber) and cases of classical tapetoretinal degeneration, since the electroretinographic responses associated with the disorders are usually indistinguishable, particularly when the onset of the visual disability remains obscure. Connatal diffuse chorioretinitis of unknown origin usually shows an ERG of subnormal or even normal qualities, and in case of a reduced electrical response the reduction is never so pronounced as described above. In diagnosing a case of amaurosis congenita in a child with some residual retinal function, one has to consider a crucial question: Is there a possibility of deterioration of the function as in the classical tapetoretinal degenerations of the retina? Up to the present we do not know whether this amaurosis congenita belongs to a dysgenesis retinalis, as Waardenburg maintains. Maybe it is better to use the expression abiotrophy, stressing the possibility of deterioration of the retinal function either in the near or distant future. In our opinion, only a painstaking survey of the reported cases followed over a period of years may supply the answer.

Although Alström and Olson did not find a higher incidence of mentally defective patients in their material than is found in the general population, our material does seem to indicate a higher incidence. Out of the 56 children discussed in the present study, 14 showed major neurologic and/or psychiatric dysfunctions (5 children suffered from epilepsy). However, the data are too incomplete to draw any definite con-

clusions at the present time. In our opinion, it will last at least one generation before we may expect to get a clearer insight into the problems mentioned above.

Summary

In the course of an investigation into causes of blindness in the Netherlands, 227 cases were found of a little-known affection: amaurosis congenita (Leber). Of these cases, 113 were in children, indicating that this affection is one of the main causes of blindness in children, at least in the Netherlands (18% of the 600 blind children known in this country). Fifty-six children were examined by us, and electroretinograms were obtained. Obligatory symptoms of the disease are connatal blindness (or deep "amblyopia"), a marked discrepancy between retinal function and fundus picture, and an incidence in blood relations typical of a recessive genetic determinant. A fourth symptom present in all cases is a modification of the ERG response—either complete absence or greatly reduced photopic activity of the retina. Occasional concomitants are nystagmus and photophobia. The incidence of cataract and keratoglobus is greater in older persons. The affection was demonstrated in 15 families. The first pedigree chart of the Netherlands, including 13 cases, stresses the heredofamiliar chara. er of this condition.

Schiedamsevest 180 (Dr. Henkes).

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Ocular Changes in Experimental Hypercholesteremia

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Cholesterol levels of 1% to 2% can be easily induced in rabbits by the simple expedient of adding cholesterol to their diet. Rabbits have little cholesterol in their diets normally, and their blood cholesterol levels are only 25 to 35 mg. % (in contrast to 100 to 250 mg. % for man). Since they do not have an effective mechanism for handling excess cholesterol, their metabolic systems may be overloaded with relative ease by adding sufficient cholesterol to their chow. Chickens may also be relatively easily overloaded with cholesterol by simple dietary means,[1] but animals which normally are exposed to considerable cholesterol in their food can handle excess cholesterol without developing hypercholesteremia unless some other factor is added. Thus, dogs may be rendered hypercholesteremic only if they are made hypothyroid,[2,3] which results in a decreased capacity for elimination of cholesterol. Rats may be made hypercholesteremic only if they are made hypothyroid and at the same time fed cholic acid.[4] The cholic acid facilitates absorption of dietary cholesterol. The monkey may be made hypercholesteremic only if, in addition to the high-cholesterol diet, he is made deficient in methionine and thereby made to lack sufficient phospholipid for mobilizing the excess cholesterol.[5] The rabbit and the chicken remain, therefore, the favorite animals for the study of hypercholesteremia because of the simplicity by which it may be induced. There is, however, no reason to doubt that comparable levels of hypercholesteremia, once attained, have similar effects in all species.

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The prime reason for interest in the hypercholesteremic rabbit, since first observed by Saltykow,[6] Ignatowski,[7] Anitschkow,[8] and Wacker and Hueck[9] is that the condition of this experimental animal is believed to represent the experimental counterpart of atherosclerosis in human beings. This thesis has been more recently developed by Leary[10] and by Katz and Stamler[11] and has been criticized by Duff and McMillan[12] and Bruger and Oppenheim.[13] The entire subject has also been most recently reviewed by Schroepfer.[14]

It is true that hypercholesteremia in human beings, in some cases at least, is associated with significantly extensive atherosclerosis. It is also true that the vascular lesions in rabbits with experimental atherosclerosis are strikingly similar to the native atherosclerosis of man. On the other hand, there is a great and significant difference in that atheromatosis in man is, with the exception of that occurring in familial hypercholesteremia, not associated with generalized xanthomatoses and reticuloendotheliosis, which is a regular feature of acute hypercholesteremia in the rabbit.

One of the prominent sites for the development of these xanthomata in the hypercholesteremic rabbit is the eye. Ophthalmologists, therefore, have a special interest in hypercholesteremia and possibly an opportunity to make a contribution to this potentially important field. Yet few descriptions of the hypercholesteremic rabbit eye have been published. Those which have been reported in any detail are those of Versé (1916 and 1924),[15,16] Rohrschneider (1925),[17] Kolen (1929),[18] and van Herwaarden (1937).[19]

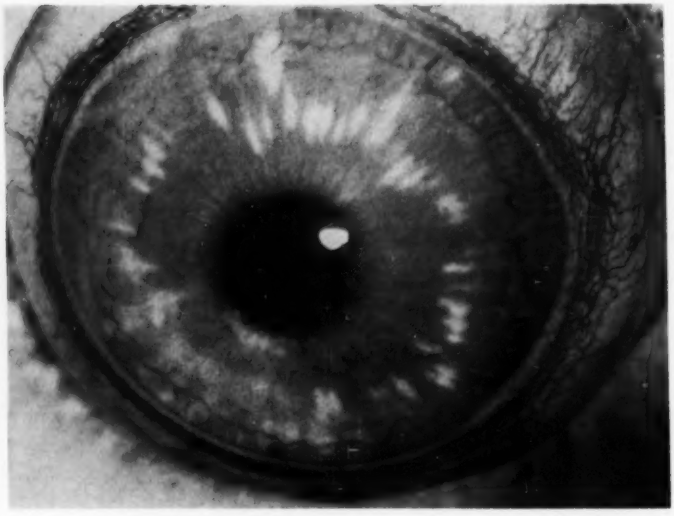

Fig. 1.—Eye of an albino rabbit which had been on a high-cholesterol diet for one year. The white plaques are in the posterior portion of the iris.

1. Specific Ocular Lesions with Experimental Hypercholesteremia (Exclusive of the So-Called Arcus Corneae)

Perhaps the most striking findings in experimental hypercholesteremia are the fatty plaques that occur on the posterior surface of the iris. Clinically these appear in albino rabbits as yellowish masses halfway between the root of the iris and pupillary margin (Fig. 1). Beginning as discrete dots, they increase in size, eventually coalesce, and may form a solid ring of opaque material (Fig. 2). Histologically they consist of masses of sudanophilic lipid and birefringent crystals. They are situated in the iris stroma but extend backward to form a tumor, projecting into the posterior chamber, covered by the iris epithelium (Fig. 3). They do not correspond to the processes which in the rabbit normally come off the iris and which are analogous to the ciliary processes in man. With sections that are passed through organic solvents and then stained with various aqueous dyes, these masses consist mostly of macrophages showing the usual foamy and periodic acid-Schiff-positive cytoplasm.

These iridic masses are obviously similar to xanthomata, but we are not aware of comparable lesions having been described in human irides.

The ciliary body in experimental hypercholesteremia also shows an abundance of sudanophilic lipid and birefringent crystals but with a distribution different from that

Fig. 2.—Eye of an albino rabbit which had been on a high-cholesterol diet for approximately two years. The white plaques have now merged into a solid ring and are partially covered by an arcus corneae in the lower nasal quadrant.

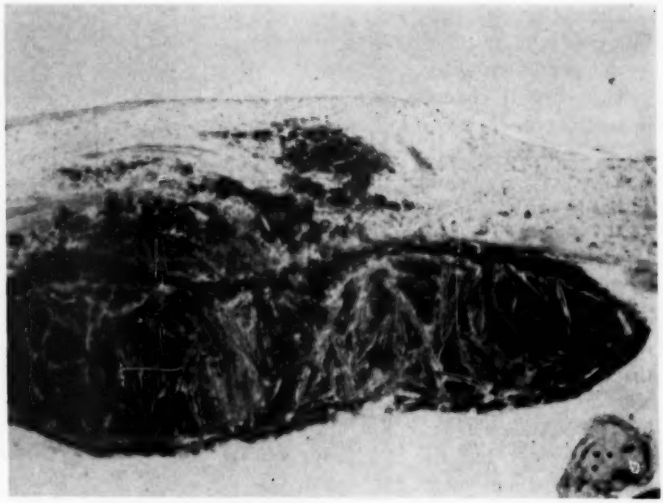

Fig. 3.—Cross section of a xanthomatous plaque of the iris stained with hematoxylin-Sudan IV. The lipid can be seen abundantly in the iris and plaque. In the latter situation there are also abundant sheaths of crystals.

in the iridic masses (Fig. 4). Immediately beneath the ciliary epithelium is a row of what we have called globular lipid arranged in spherules as large as 20μ, mostly within cells. Deep to this is a variable amount of fine lipid which we have called granular sudanophilia; most of this is extracellular. The ciliary processes contain a scattering of globular lipid chiefly in association with blood vessels and never extensive.

Overlying the ciliary body and involving the deep sclera extensively is a great abundance of globular sudanophilia and birefringent material. This may be so abundant as to thicken the sclera one to two times and sometimes presents as an episcleral tumor. The lipid is characteristically intracellular, and defatted sections show masses of foam cells similar to those seen in xanthomata. The choroid shows moderate infiltration with similar lipid material and with involvement of the overlying sclera, but the choroid is perhaps less involved than would be expected on the basis of its vascularity.

Fig. 4.—Cross section through the ciliary body stained with hematoxylin-Sudan IV. Noteworthy is the abundance of globular and granular sudanophilia, with a row of the former situated just beneath the epithelium.

The retina and optic nerve show no infiltration with fat, and there is no free fat in the subretinal space.

The corneal changes will be presented in the subsequent section in connection with arcus corneae, but it may be noteworthy that a diffuse sudanophilia is apt to be found characteristically just in front of the angle meshwork. The significance of this is obscure.

While these changes in the eyes of hypercholesteremic rabbits are not known to exist in human pathology, it must be admitted that there is little, if any, information available on the ocular changes with such high hypercholesteremia in human beings. We have, however, had the opportunity to follow one patient with familial hypercholesteremia who has had recurrent bilateral scleritis for years accompanied by visible fat in the peripheral cornea and angle of the anterior chamber.

For what it is worth, it may also be noted that many of the changes in the experimental rabbit eye simulate those which occur with that type of xanthomatosis of the skin that is often associated with hypercholesteremia. On the other hand, the lesions tend to contain more lipid and are less densely cellular than is found with the lesions of the so-called primary xanthomatoses.

2. Hypercholesteremic Arcus Corneae and Arcus Senilis

A relationship between the ordinary arcus senilis and cholesterol levels in the blood was suggested as early as 1911 [20] and has been reaffirmed several times since,[21] but the relationship, if any, is certainly not a straight-line function. Yet the fact that patients with idiopathic hypercholesteremia have a conspicuous arcus (Fig. 5), even at an early age, has indicated some sort of tie-up.[22] It is, therefore, not surprising that the arcus which hypercholesteremic rabbits develop after being on the diet a few months has been generally interpreted as the experimental counterpart of arcus senilis in man (Versé,[15,16] Rohrschneider,[17] Kaiser,[23] and Forsius [24]). It is our purpose, however, to point out that the arcus in experimental hypercholesteremia is similar to arcus senilis in superficial respects only. The differences so far outweigh the similarities that it is improper to analogize the two on the basis of our current knowledge.

Fig. 5.—Arcus senilis in a patient with familial hypercholesteremia. These arcuses occurring in human beings are not vascularized; they involve the full thickness of the cornea, and they are separated from the limbus by a relatively clear area.

On clinical grounds the arcus of hypercholesteremic rabbits differs from that of human beings in that it is situated entirely, or nearly entirely, in the superficial cornea; there is no sparing of the paralimbal region; it is always vascularized, and it contains an abundance of what appear to be scintillating crystals (Fig. 6).

On pathologic grounds the differences are even more striking. The characteristic histologic findings of arcus senilis in human beings are a diffuse sudanophilia of the peripheral portions of Bowman's and Descemet's membranes and a granular sudanophilia of the limbal portions of the entire thickness of the corneal stroma (Fig. 7). The lipid is entirely extracellular; it is not accompanied by any other morphologic change in the cornea, and characteristically it spares the region in immediate proximity to blood vessels.

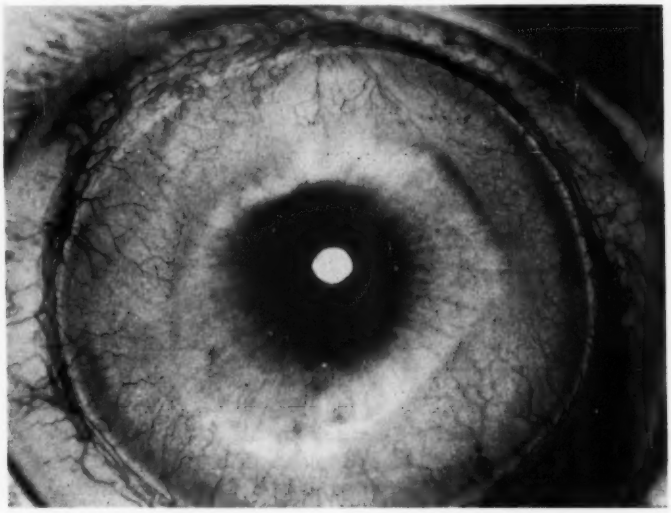

Fig. 6.—Arcus in a rabbit which has had a severe hypercholesteremia for several months. The arcus is characteristically vascularized, involves only the anterior portion of the stroma, and is continuous with the limbus. In the present photograph it obscures the plaques of of the iris.

In contrast to this, the arcus of rabbits does not involve preferentially Bowman's membrane (which the rabbit *does* have, despite statements to the contrary) or Descemet's membrane and the stromal changes consist primarily of a *globular intra*cellular lipid situated in the most superficial layers of the cornea, accompanied by considerable histiocytosis (Fig. 8). It is true, however, that one may also find a diffuse scattering of granular sudanophilia in the peripheral cornea similar to that in humans, but this is infrequent and is not accompanied by sudanophilia of Descemet's membrane, which is the most conspicuous manifestation in human beings. On the other hand, the changes in the corneas of the hypercholesteremic rabbit are similar to those which occur following injection of hypercholesteremic serum directly into rabbit corneas.

3. Site of Xanthomatous Plaques and Trauma

In systemic xanthomatosis of human beings lipid plaques have been noted to occur at sites of trauma both in the skin [25] and in the eye.[26] Injury to the cornea of hyper-

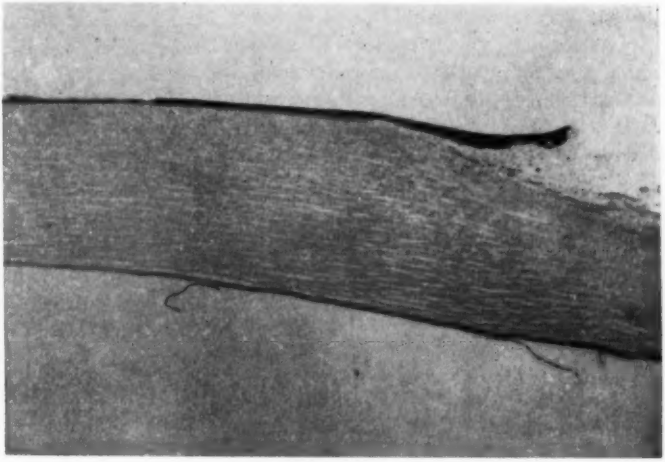

Fig. 7.—Arcus senilis in a human being showing diffuse and granular sudanophilia of the entire stroma, with particularly intense sudanophilia of Bowman's and Descemet's membranes.

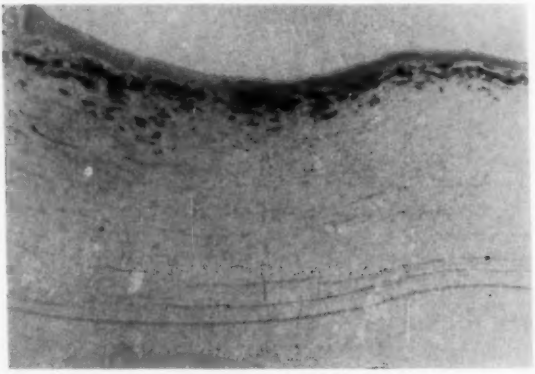

Fig. 8.—Arcus in hypercholesteremic rabbit, showing globular sudanophilia (intracellular) in the anterior portion of corneal stroma.

cholesteremic rabbits has also been found to cause a marked increase of the arcus in this area.[19,27] Forms of trauma to the eye which we have used are thermal cautery of the cornea, diathermy cautery of the sclera, and manipulation of a magnetic "flea" which had been inserted into the anterior chamber according to a technique which has previously been described.[28] We have also had occasion to study the effects on other tissue which we have incidentally traumatized.

The results are clear-cut. Injury results in the development of a plaque which has the essential characteristics of a xanthoma. In the cornea the plaque appears to be associated with abnormal vascularity and will occur to some extent if the cornea has been vascularized prior to the hypercholesteremia but is much more marked if the neovasculogenesis occurs while the animal is hypercholesteremic.* This is obviously analogous to the plaques which occur occasionally in human beings, previously called lipidosis corneae.[29] The plaques in human beings develop with remarkable rapidity in areas of prior vascularization and are thought to coincide with surges of hypercholesteremia or hyperlipemia and to be analogous to atheromatous plaques in blood vessel walls.[30]

Manipulation of a metallic "flea" in the anterior chamber results in a local increase in the arcus of the *superficial* portions of the cornea and also, interestingly, an increase in the xanthomatous plaques in the posterior portion of the iris of the sector corresponding to the manipulation. Since the "flea" is not in contact with the iris except at the root and does not traumatize the iris during manipulation, the appearance of the xanthomata in this sector suggests that the cause of the plaques is alteration in permeability of the vessels rather than a direct result of injury. Similar conclusions might be drawn from the fact[27] that injury to the periphery of the cornea results in a local increase in the arcus whereas injury to the center of the cornea does not.

Diathermy to the sclera over the region of the equator was done to determine whether or not a condition might be induced that simulated Coats' disease. This was found not to be the case, but a great increase in the deposition of lipid in the sclera did occur, with the development of large white plaques in the ophthalmoscopic view.

Perhaps the most striking illustration of xanthoma-like localization with trauma was that which was incidentally observed in the heart. We had done several cardiac punctures in different animals to obtain blood. The hypercholesteremic animals were found at autopsy to have discrete plaques on the epicardium and a yellowish-white streak extending therefrom into the ventricle at the sites of puncture. These plaques and tracts contained masses of sudanophilic lipid and birefringent material which on defatted sections were seen to be composed chiefly of foam cells and macrophages.

* See Figure 5 in Cogan and Kuwabara.[30]

Comments and Conclusions

Experimental hypercholesteremia results in xanthoma-like lesions in the eyes of rabbits. Comparable lesions in human eyes, suggested by some clinical observations, have as yet been only partially described in pathologic specimens. Contrary to the general impression, the arcus of the hypercholesteremic rabbit appears to be very different from arcus senilis of man. On the other hand, traumatically induced, xanthomatous plaques in the hypercholesteremic rabbit cornea (and elsewhere) are most suggestively similar to lipid plaques occurring in the cornea of man.

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Practical Management of Granulomatous Chorioretinitis

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Since the discovery of Toxoplasma in lesions of chorioretinitis, its importance as a causative agent is being increasingly recognized. The criteria for its diagnosis are (1) compatible ocular picture, (2) positive Feldman-Sabin dye test in a minimum titer of 1:64, (3) positive toxoplasmin skin test, (4) exclusion of other granulomatous disease, and (5) a favorable response to antitoxoplasmic therapy.[1] Of these criteria, only the performance of the dye test presents difficulties for the practicing ophthalmologist. The technical difficulties of the test enable only a few laboratories to perform it in limited quantities, and the results, therefore, are not available to most physicians within a few days. By relying on the toxoplasmin skin test, however, a presumptive diagnosis can be entertained and early treatment begun.

Presented here is a review of consecutive cases of granulomatous chorioretinitis seen by us from January, 1956, to March, 1958. The evaluation consisted of a complete physical exmaination, survey for foci of infection, x-rays of the chest and paranasal sinuses, stool studies, and skin tests for tuberculosis and toxoplasmosis. Presumptive diagnosis of toxoplasmosis was made on the basis of a negative past history and physical examination, a strongly positive toxoplasmin skin test, negative P. P. D. No. 1 skin test, and negative x-ray of the chest. Tuberculous etiology was presumed with a history of tuberculosis or x-ray evidence of healed tuberculosis, or a positive P. P. D. No. 1 and a negative or slightly positive toxoplasmin skin test. Ophthalmoscopic appearance of chorioretinitis due to the various causative agents is not sufficiently distinctive to permit differential diagnosis.

The treatment for presumed toxoplasmic etiology in our cases consisted of 50 to 75 mg. of pyrimethamine (Daraprim, Burroughs-Wellcome) and 2 to 3 gm. of sulfadiazine per day, in divided doses, for a period of three weeks, then 25 mg. of pyrimethamine and 1 gm. of sulfadiazine per day for three additional weeks. Therapeutic response was either an unequivocal diminution of the exudation within 7 to 10 days or a rapid increase in vitreous debris within 3 to 7 days, the latter being presumably due to breaking up of pseudocysts, resulting in increased tissue reaction.[2,3] In this latter instance steroids were added to the therapeutic regimen: cortisone, 300 mg. daily, initially, and 100 mg. daily for maintenance, or prednisone, 30 mg. daily, initially, and 20 mg. daily for maintenance; rapid response was expected within 7 to 10 days. Lack of rapid and unquestionable improvement indicated that the presumptive etiologic diagnosis was erroneous, and another regimen was tried in accordance with the diagnostic work-up. Concomitant steroids were used at the outset when the lesion was in the macular or paramacular area.

In the management of tuberculous uveitis, our treatment consisted of 0.5 gm. each of streptomycin and dihydrostreptomycin twice weekly, along with 300 mg. of isoniazid daily for a minimum of four months. The response in this group was much slower, becoming definite only after four to six weeks of therapy.

Table 1 presents 32 patients treated with a presumptive diagnosis of toxoplasmosis. It will be noted that the majority were

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TABLE 1.—*Presumptive Toxoplasmic Etiology*

Case	Sex	Age, Yr.	Vision	Ocular Lesion	Vitreous Reaction	P. P. D. No. 1	Toxoplasmin Skin Test	Antitoxo. Therapy, Wk.	Final Vision	Follow-Up, Mo.	Result
1	M	21	20/20	Recurrent, O. S.	Mild	Neg.	2+	6	20/20	16	Excel.
2	M	32	20/100	New, O. D.	Severe	Neg.	2+	6	20/40	1	Excel.
3	M	36	20/25	Inflam. ret. det., O. D.	Mild	Neg.	4+	4	20/20	6	Poor
4	M	20	20/20	Recurrent, O. D.	Mild	Neg.	3+	6	20/20	1	Excel.
5	M	25	LP	Recurrent, O. D.	Severe	Neg.	3+	6	20/20	17	Excel.
6	M	19	20/20	Recurrent, O. D.	Moderate	Neg.	2+	6	20/20	2	Excel.
7	F	31	20/30	Recurrent, O. S.	Moderate	Neg.	3+	6+steroids	20/20	8	Excel.
8	M	19	8/200	Recurrent, O. D. macular	Mild	Neg.	1+	6	20/200	7	Excel.
9	M	20	20/200	Recurrent, O. D. macular	Moderate	Neg.	4+	6+ steroids	20/200	3	Excel.
10	M	18	20/30	New, O. D.	Mild	Neg.	4+	6+steroids	20/20	4	Excel.
11	M	20	20/25	Recurrent, O. D.	Mild	Neg.	2+	6	20/20	3	Excel.
12	M	20	20/20	Recurrent, O. S.	Moderate	Neg.	4+	6+steroids	20/20	1	Excel.
13	F	22	20/25	Recurrent, O. D.	Mild	Neg.	3+	6	20/20	15	Excel.
14	M	28	20/80	Recurrent, O. S.	Severe	Neg.	2+	6	20/20	10	Excel.
15	M	19	20/30	Recurrent, O. D.	Mild	Neg.	2+	4+steroids	20/60	—	Poor
16	F	27	20/160	Recurrent, O. D. macular	Mild	Neg.	2+	6+steroids	20/25	10	Excel.
17	M	22	20/70	Recurrent, O. D. 2d cataract	Mild	Neg.	1+	6+steroids	20/70	6	Poor
18	M	30	20/20	Recurrent, O. D.	Mild	Neg.	3+	6	20/20	11	Excel.
19	M	35	20/50	New, O. D.	Severe	Neg.	2+	6+steroids	20/30	1	Excel.
20	M	25	20/80	Recurrent, O. D.	Severe	Neg.	2+	4+steroids	20/20	3	Excel.
21	F	37	20/200	New, O. D. macular	Mild	Neg.	2+	2+steroids	20/80	—	Poor
22	F	48	20/40	Recurrent, O. S.	Moderate	Neg.	2+	6+steroids	20/20	8	Excel.
23	F	23	20/80	Recurrent, O. S. Gl and cat.	Moderate	Neg.	2+	6+steroids	20/200	8	Poor
24	F	34	20/20	Recurrent, O. D.	Moderate	Neg.	3+	6	20/20	5	Excel.
25	M	18	2/200	Recurrent, O. S. macular	Mild	Neg.	2+	6	10/200	4	Excel.
26	M	26	20/20	Recurrent, O. D.	Mild	Neg.	2+	6+steroids	20/20	1	Excel.
27	M	19	LP	Recurrent, O. D. periphlebitis	Severe	Neg.	3+	6+steroids	20/40	3	Excel.
28	F	21	20/60	Periphlebitis, O. S.	Severe	Neg.	3+	4+steroids	20/20	—	Undet.
29	M	36	20/50	Recurrent, O. D.	Moderate	Neg.	3+	6	20/20	4	Excel.
30	M	21	20/200	Recurrent, O. D. macular	Mild	Neg.	1+	6+steroids	20/30	6	Excel.
31	M	32	20/20	Recurrent, O. D.	Mild	Neg.	3+	6	20/20	1	Excel.
32	M	35	20/30	Recurrent, O. S.	Mild	Neg.	2+	6	20/20	5	Excel.
33	M	27	20/50	Recurrent, O. S.	Severe	Neg.	2+	6+steroids	20/20	2	Excel.
34	M	32	20/20	Recurrent, O. S.	Mild	Neg.	1+	6	20/20	2	Excel.
35	M	19	20/20	New, O. S.	Mild	Neg.	2+	6	20/20	1	Excel.
36	M	18	20/20	Recurrent, O. S.	Mild	Neg.	3+	6	20/20	1	Excel.

recurrent acute inflammatory lesions adjacent to old chorioretinal scars. Of the thirty-two, twenty-six are considered to have had excellent therapeutic results, in that there was a rapid ophthalmoscopic subsidence of the retinal exudation and of the edema, gradual disappearance of the vitreous debris, return of visual acuity in peripheral infections, and progressive pigment deposition. The therapeutic response was not proportional to the positivity of the skin test.

Table 2 presents four cases which were initially treated with a presumptive diagnosis of toxoplasmic etiology, but upon lack of satisfactory response within 7 to 10 days, antituberculous treatment was substituted. All of these responded well to the latter therapy.

Table 3 shows four cases presumed to be due to tuberculosis. Of these, three showed excellent results and one showed no significant improvement.

In this series we had only one serious hematologic reaction to pyrimethamine and sulfadiazine. This developed when the concurrent systemic steroid therapy was being withdrawn, indicating the masking effect of steroids on toxic bone marrow depression.

TABLE 2.—*Erroneous Presumptive Toxoplasmic Etiology*

Case	Sex	Age, Yr.	Vision	Ocular Lesion	Vitreous Reaction	P. P. D. No. 2	Toxoplasmin Skin Test	Antitoxo. Therapy, Wk.	Antituberc. Therapy, Mo.	Final Vision	Follow-Up, Mo.	Result
1	F	23	20/20 O. U.	Recurrent, bilateral	Moderate	2+	2+	6+steroids	6	20/20 O. U.	2	Excel.
2	M	22	20/25	Recurrent, O. S.	Mild	2+	3+	4+steroids	4	20/20	1	Excel.
3	F	24	20/70	Recurrent, O. S.	Severe	2+	2+	2+steroids	4	20/20	4	Excel.
4	M	23	20/40	Periphlebitis, O. D.	Severe	2+	3+	5+steroids	4	20/20	3	Excel.

The patient responded rapidly to discontinuance of the drugs and corticotropin (ACTH). Minor skin reactions were encountered in three patients, but they responded to steroids without discontinuation of pyrimethamine.

Comment

The complete diagnostic work-up for uveitis is not available to the average ophthalmologist, because the Feldman-Sabin dye test and the complement-fixation tests are performed by too few laboratories.[4] The danger of laboratory infections and the delicateness of these tests make it unlikely that they will become readily accessible. Furthermore, the advantages of early treatment are obvious and diagnostic tests lasting over a few days are definitely handicapping.

The simplicity, potential availability, and rapid results of the toxoplasmin skin test recommend it to the ophthalmologist. Although positive skin tests are found in the normal population, the substantially higher proportion of positive tests in patients with granulomatous uveitis justifies a therapeutic trial.[3] As success or failure of the therapeutic trial becomes manifested rapidly, little time need be lost in case of failure, and one may try another approach.

In this series excellent results were obtained in 81% of the eyes, which, within the limitations of brief follow-up in many of the cases, appears to justify the reliance on the toxoplasmin and tuberculin skin tests.

Conclusions

In the practical management of posterior granulomatous uveitis, the toxoplasmin and P. P. D. skin tests are very valuable diagnostic tools for formulating a presumptive etiologic diagnosis.

In the therapy for presumed toxoplasmosis, pyrimethamine (Daraprim) and sulfadiazine give excellent results. Systemic steroids are valuable adjuncts in the treatment of toxoplasmic perimacular lesions and "hypersensitive reactions."

Inadequate response to antitoxoplasmic therapy in the presence of positive P. P. D. test warrants antituberculous chemotherapy.

Dr. Leon Jacobs, National Institutes of Health, Bethesda, Md., furnished the toxoplasmin and the control antigens.

Tripler U. S. Army Hospital.

TABLE 3.—*Presumptive Tuberculous Etiology*

Case	Sex	Age, Yr.	Vision	Ocular Vision	Vitreous Reaction	P. P. D.	Toxoplasmin Skin Test	Antituberc. Therapy, Mo.	Final Vision	Follow-Up, Mo.	Result
1	M	19	20/30	O. S. focal choroiditis	Mild	No. 2, 2+	1+	4	20/20	1	Excel.
2	M	37	20/30 O. U.	Bilateral periphlebitis	Mild	No. 2, 4+	Neg.	4	20/20 O. U.	2	Excel.
3	F	40	10/200	Recurrent, O. S. macular	Mild	Tubere. pt.	2+	4	10/200	2	Excel.
4	M	23	20/20	Recurrent, O. D.	Mild	No. 2, 2+	Neg.	8	20/50	—	Poor

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Afterimages and Ocular Muscle Proprioception

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Adler stated in his textbook of physiology that afterimages arise from photochemical processes in the retina and are of peripheral origin. He stated, "It cannot be denied that central processes may exert inhibitory influences on afterimages, but it seems certain that they do not take their origin in the higher centers." [1] He also stated, "It is still being debated how effective proprioceptive impulses, coming from the ocular muscles, are in determining the position of the eyes in the orbit and in relation to one another." [2]

While experimenting with the movement of afterimages I noticed certain phenomena that could only be explained by the central origin of afterimages and the effectiveness of ocular muscle proprioception. In this paper three experiments will be presented and discussed. The subjects and observers in these experiments were five residents in ophthalmology at the Illinois Eye and Ear Infirmary, and they all reported the same findings, which are given below.

1. Afterimages Seen with Ocular Movements and Head Movements

The subjects were made to look at a vertical light, such as that used in the Bielschowsky afterimage test, with both eyes open, for a period sufficient to give a strong afterimage. With both eyes open, looking at a wall straight ahead, a vertical afterimage was seen straight ahead. On turning the eyes left, right, up, or down the afterimage was seen to move in the direction of the eye movements.

Next, keeping the eyes stationary in the orbit so that they moved with the movement of the head, the head was turned to the right, left, up, or down, and the afterimage was seen to move in the same direction as the head was turned. On tilting the head to the right or left shoulder, the afterimage tilted in the same direction as the head. With the eyes closed, repeating the movements above, that is, moving only the eyes and then moving only the head, it was noticed that the afterimages moved exactly as they did when the eyes were open.

When a vertical afterimage was induced in only one eye, it was seen that the afterimage again moved in the direction in which the eyes or head voluntarily moved. But if the eye experiencing the afterimage was moved passively, e. g., pushed with a finger, no movement of the afterimage occurred either with the eyes open or shut.

Comment.—What are the physiological principles that explain the synchronous movements of the afterimages with the eye and head movements? The accepted explanation has been that when we look at a light, afterimages are formed on the macula by local photochemical processes, and, in whatever direction the macula looks, the afterimages would be projected. This is well and good for the projection of the images with the eyes open, but what about the projection with the eyes closed? Certainly with the eyes closed the maculae do not take part in space orientation. With the eyes closed we can only know in what direction the eyes or head are turned because of the knowledge of the willed movement and because of ocular proprioception in eye movements and neck muscle proprioception in head movements. "It does not depend on sensory impulses from the lids and conjunctiva, for these can be completely anes-

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thetized without interfering with the senses of position of the globe." [3]

The projection of the afterimages then would be determined by proprioception of the ocular movements. This, however, would still not rule out the local retinal formation of the afterimages. But, the observation that there was no movement of the afterimage when the eye was moved passively was of great significance. For, since no movement occurred, it would be most unlikely for them to be of peripheral retinal origin, since one would expect that, if they were, any movement of the retina, either active or passive, would result in corresponding movement of the afterimage. The only reasonable explanation in the light of these facts would be that they are of cerebral origin.

2. Afterimage Findings in Induced Nystagmus

a. Vestibular Nystagmus.—In this experiment a distinct vertical afterimage was induced by looking at a vertical light. The subject was seated in the Barany chair with the head bent forward slightly to stimulate the horizontal semicircular canals. The gaze was directed straight ahead, and the afterimage was seen in the same direction. The chair was started suddenly, rotated rapidly for a while, and stopped suddenly. The following phenomena were noted: When the chair was suddenly rotated to the right, the eyes deviated to the left. The subject was aware of the direction of the deviation with the eyes open or shut, and he saw the afterimage deviate to the left. When the chair was suddenly stopped, the eyes deviated to the right; the subject was aware of the direction of deviation whether the eyes were open or closed, and the afterimage was seen to the right. However, when an observer looked at the subject's eyes immediately after the chair was stopped, marked horizontal nystagmus was seen of which the subject was unaware. No back-and-forth movement of the afterimage was seen (corresponding with the nystagmus).

b. Opticokinetic Nystagmus.—A vertical afterimage was induced in both eyes, and the subject looked at a rotating drum with alternating vertical black and white stripes. He stated that he felt his eyes turning (which they did) and that he saw the afterimage in the direction of the rotation of the drum. Even though a marked horizontal opticokinetic nystagmus was present as seen by the observer, at no time was the subject aware of the nystagmus or of a corresponding oscillation of the afterimage.

Comment.—In both the chair- and drum-rotation experiments the afterimage was seen in the direction in which the subject was aware that his eyes had turned. He was unaware of the nystagmus, and thus he did not see a back-and-forth movement of the afterimage. Cases of spontaneous nystagmus also are unaware of their ocular movement. These findings indicate that the projection of afterimages is determined by ocular muscle proprioception. As a corollary to this, the unawareness of the back-and-forth movement of the eyes in nystagmus would indicate that there is no proprioception present for this condition.

3. Changes in the Size of the Afterimages

A round afterimage was induced by looking at a 60 watt incandescent bulb. The subject looked at a wall about 10 ft. away. It was noted that an afterimage of a certain size was seen. Then the gaze was directed at a wall 20 ft. away and the afterimage increased in size. Finally, when the subject looked at a sheet of paper 10 in. from the eyes, the afterimage became very small. Surprisingly enough, the same phenomenon was observed with the eyes closed. This was done by the subject keeping his eyes closed and imagining that he was converging on his finger held 15 in. from his eyes. The afterimage was seen to be small. Then, with the eyes still closed, imagining he was looking out in the distance, he noticed that the afterimage became much larger.

Comment.—How can the change in size of the afterimage as one looks at different

distances be explained? In ordinary sight, an object producing a certain-sized image on the retina must become increasingly larger the farther away it is from the eyes in order to produce the same-sized retinal image. This is simple geometrical optics. Now if a certain area of the retina is stimulated or dazzled, as by a local retinal lesion, as one looked in the distance one could expect the area of dazzle to appear larger. The area of dazzle, as measured on the tangent screen would become proportionately larger as the tangent screen was moved away. Thus the change in the size of the afterimages, if they were of local retinal origin, observed for different distances with the eyes open would be easy to explain.

How can the size changes be explained when the eyes are shut? They cannot be explained by the theory which states that afterimages are of retinal origin, since there is no retinal space orientation with the eyes closed. They can be rationally explained if one postulates that (1) afterimages are of cerebral origin, and (2) proprioception for convergence and divergence of the eyes exists. The explanation is as follows: the cortex, being the seat of origin of the afterimage, has developed a conditioned reflex, relative to the size of the afterimages and based on proprioception. When it receives the proprioception impulses for convergence (because of past experience that closer objects are smaller than distant objects of the same image size), it will project a small afterimage. When the sensation of divergence is perceived (through past experience that distant objects are larger than closer objects of the same image size), a larger afterimage will be projected.

Along the same lines, Chavasse did the following experiment with afterimages.[4] He produced an afterimage in both eyes by gazing at a very bright light in the distance. He found that with convergence the afterimage approached and with divergence it receded. He felt that this finding was evidence for the presence of proprioception for convergence and divergence.

Summary

Evidence for the cerebral origin of afterimages is presented.

Ocular proprioception was found for voluntary eye movements and for eye movements in the direction of the slow component in induced nystagmus. With awareness of these movements afterimages were correctly projected.

No ocular proprioception was found for passive eye movements and for the back-and-forth movements of induced nystagmus. As a result, with no awareness of movement, no projection of the afterimages occurred.

Ocular proprioception was found for divergence and convergence, with the afterimages becoming smaller in convergence and larger in divergence.

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Studies on the Antibacterial Properties of Human Vitreous

A Preliminary Report

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There has been a tremendous amount of work done throughout the years on the anatomical and physiological structure of the vitreous, and a great deal has been done toward understanding its metabolic processes. It is more difficult, however, to find much in the literature on the question of whether or not vitreous is a good culture medium. In the older textbooks of ophthalmology [1] vitreous is considered to be a good culture medium, and even the more recent textbooks [2] make this assumption. The rapidity with which an intraocular infection will spread through the vitreous is usually cited as evidence for this point of view.

With Shafer's [3] introduction of human vitreous implant as an adjunct to diathermy in the treatment of retinal detachment, there was an increase of interest in this problem. At The Eye Bank for Sight Restoration, where a program for the aspiration and storage of human vitreous was begun by Milo H. Fritz and developed by Shafer, vitreous is aspirated from Eye Bank eyes in which the cornea is judged unsuitable for keratoplasty. For this reason, vitreous aspiration is usually accomplished between 48 and 72 hours after the death of the donor.

The vitreous is withdrawn with use of an aseptic technique [3] and stored in the refrigerator at 4 C. It is not cultured at the time of aspiration, but it is held until needed and cultured at least 48 hours before use. The policy is to keep four vials, each containing from 2 to 6 cc., cultured and ready for use.

The consistently negative results of these cultures led Shafer to question the old belief that vitreous was a good culture medium. Furthermore, on the few occasions when one or two colonies appeared on the agar plate, reculture of the same vial of vitreous was invariably negative.

To test vitreous as a culture medium Shafer contaminated sterile samples of vitreous by stroking a cotton swab through a hemolytic Staphlococcus pyogenes var. aureus colony and plunging the swab into the vial of vitreous. This was refrigerated at 4 C and cultured after 48 hours. He found that even after contamination the vitreous was sterile in 48 hours. Other workers began to question this method, and at least one group had similar findings. Reed et al.[4] found that human vitreous had self-sterilizing properties. The rate of self-sterilization varied with the different organisms and in proportion to the amount used in the contamination. The only organism of the seven checked in their study that was not destroyed in the vitreous was Bacillus subtilis. The fact that this was a spore-forming bacillus was considered sufficient explanation as to why the organisms could survive. They did not find the same "antibacterial property" in dog or rabbit vitreous. Colvin [5] reported that the Burroughs-Wellcome Laboratories in England were unable to find any self-sterilization property in horse vitreous. In the light of Reed's work, this could have been due either to the amount of bacteria used and the comparatively short time lapse before the

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vitreous was recultured or to a difference between horse and human vitreous. Suie and Sroufe,[7] in their preliminary study, found no antibacterial in human vitreous. In their studies, the contaminated vitreous was incubated at 37 C and cultured in 24 hours. Here again the question of time is raised, and the factor of temperature is an added consideration.

All workers do agree in one point: Whether the vitreous possesses any self-sterilization properties or not, the utmost care should be taken for the aseptic aspiration, storage, and use of vitreous in implantation.

This search of the available literature still left the question of self-sterilization of vitreous with unsatisfactory or contradictory answers. With this in mind, the following study was undertaken.

Procedures

The first problem to be considered was the determination of the number of organisms to be used in the contamination of the vitreous.* Of the various acknowledged methods, the one chosen was a modified serial dilution technique that was used in early studies on penicillin sensitivities. A pure colony of S. pyogenes var. aureus was streaked on blood agar plate and incubated at 37.5 C for 24 hours. A fresh colony was removed with a loop from this plate and placed in 3 cc. of beef broth; the broth was incubated at 37.5 C for three hours, after which 1 cc. of the contaminated broth was withdrawn and placed in a 50 cc. bottle of sterile broth. This gave a broth that was believed to contain 250,000 organisms per cubic centimeter. This was subsequently diluted to a strength of 2,500 organisms per cubic centimeter, or 250 organisms in each 0.1 cc.

To check the accuracy of these dilutions, 0.1 cc. of the three-hour seeded broth was used in the pour-plate method. The results indicated that our dilutions had less than 10% error. This was not considered excessive or greater than would be found by any other counting method.

Having established the method of estimating the number of organisms to be used in contamination, the next problem was the vitreous to be used. Since our aim was to test vitreous collected and stored by our methods, we used vitreous from the Eye Bank collection of stored vitreous. For comparison, we also used some freshly aspirated vitreous which was cultured at the time of aspiration.

In the first series of tests, two vials of stored vitreous, two vials of fresh vitreous, and two tubes of sterile broth were contaminated with equal amounts of seeded broth. One set of stored and fresh vitreous and control broth was placed in the refrigerator (4 C), the other, in the incubator (37.5 C). After 48 hours each was cultured on blood agar, and the plates were read after another 48 hours at 37.5 C.

Later, since there appeared to be no difference between the stored and the fresh vitreous, the use of fresh vitreous was abandoned as unnecessary duplication.

To rule out the possibility that the seeding beef broth gave an added nutrient factor not found in the vitreous, a number of tests were done with 1 cc. of the seeded three-hour broth in 50 cc. of isotonic saline, taking the same aliquot from this for the contamination of the vitreous. In the 48-hour period of incubation, the results with use of the saline dilutant were the same as those obtained when beef broth was used.

Results

Table 1 shows the results of the contamination at concentrations of from 500 to 25,000 organisms in vials containing 2 to 2.5 cc. of vitreous. Refrigerated specimens are compared with the incubated specimens and with the control broths.

Vitreous was from individual eyes and was not pooled. We are aware that the number of samples in this study may be considered small from a statistical stand-

* Mrs. B. Fitzpatrick, of the Pathology Laboratory of Manhattan Eye, Ear, and Throat Hospital, gave technical assistance.

TABLE 1.—*Staphylococcus Pyogenes Var. Aureus*

Organisms, No.	Incubated Vitreous	Incubated Broth	Refrigerated Vitreous	Refrigerated Broth
25,000	Growth	Growth	Growth	Growth
2,500	Growth	Growth	Growth	Growth
1,500	Growth	Growth	No growth	Growth
1,500 *	Growth	Growth	No growth	Growth
500 †	No growth	Growth	No growth	Growth

* Vials from this series were kept and recultured at regular intervals. The refrigerated vitreous continued sterile; the incubated vitreous was still contaminated after 1 week, but was sterile 2 weeks after contamination. The incubated broth showed less growth at the end of 2 weeks than the refrigerated broth.

† One vial in this series showed light growth after 48 hours. Recultured 7 days later, it was sterile.

point, but the supply of human vitreous is limited and the demand is great, and so the amount available for use in this study was restricted.

The major portion of this study was done with one strain of S. pyogenes var. aureus (hemolytic, mannitol-positive) obtained from the cul-de-sac of an eye patient. Since this organism is so common in the eye, it was considered a good one for the series. A smaller study was done with the real villain to the ophthalmologist and the eye, Pseudomonas aeruginosa. These findings are recorded in Table 2. Because of the rapid spreading nature of growth of this organism, we could not determine the number of organisms used in the contaminations, but we innoculated a fresh broth with a loop full of Pseudomonas and incubated it for about three hours, or until turbid; 0.2 cc. of this suspension was then innoculated into the vial of sterile vitreous.

The difference between the results with use of Staphylococcus as a contaminant and the results when Pseudomonas was used led us to question which bacteria might show a growth inhibition in vitreous and which might not. Was the fact that Staphylococcus did not grow in vitreous in the lower dilutions owing to a bacteriostatic effect, or was it due to lack of sufficient metabolites?

TABLE 2.—*Pseudomonas Aeruginosa* *

Incubated Vitreous	Incubated Broth	Refrigerated Vitreous	Refrigerated Broth
Growth	Growth	Growth	Growth

* Massive contaminations by undetermined number of organisms.

A new series of experiments was initiated. A 6 mm. plug was removed from a blood agar plate; the plate was liberally seeded with a given organism, and the well was filled with about 0.2 cc. of refrigerated sterile vitreous. The plates were checked at 24 and 48 hours for growth and the presence of any zone of inhibition. On some of the plates we placed two sterile discs impregnated with antibiotics, so that we could compare the zones of inhibition.

There was a definite zone of inhibited growth around the pool of vitreous on both of the plates seeded with different strains of S. pyogenes var. aureus (Figs. 1 and 2). The plate seeded with Koch-Weeks bacillus (Fig. 3) also showed a large distinct zone of inhibition around the vitreous. The first plates seeded with Proteus vulgaris and Pseudomonas aeruginosa showed only the slightest suggestion of inhibited growth, so they were repeated. This time we seeded the plates more lightly. The results, a definite zone of inhibition on the Proteus plate

Fig. 1.—A large zone of inhibition appears around the pool of vitreous on the first plate seeded with Staphylococcus pyogenes var. aureus. In subsequent plates discs impregnated with antibiotics were added for comparison.

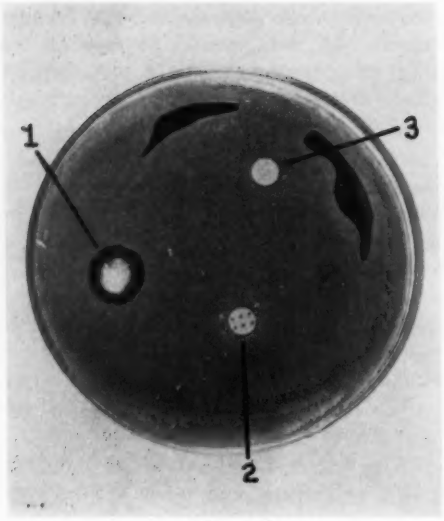


Figure 2

Fig. 2.—Agar plate seeded with Staphylococcus aureus. Note zone of inhibition around vitreous (*1*) and the absence of inhibition around discs impregnated with polymyxin (*2*) and tetracycline (Achromycin) (*3*).

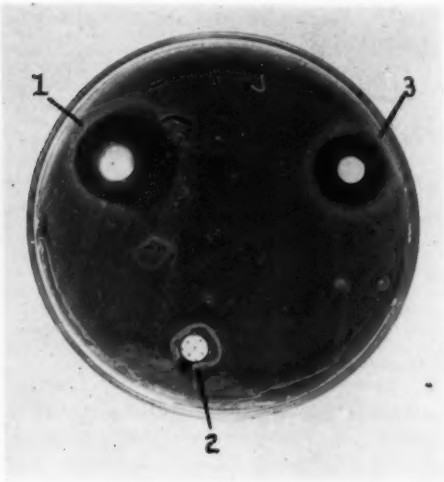


Figure 3

Fig. 3.—Agar plate seeded with Koch-Weeks bacillus. Zone of inhibited growth around vitreous (*1*) is greater than that around tetracycline (Achromycin) disc (*3*), and there is almost no sign of inhibition around the polymyxin disc (*2*).

Fig. 4.—Agar plate seeded with Proteus vulgaris. The largest zone of inhibited growth is around the vitreous (*1*). The neomycin-impregnated disc (*3*) also shows definite inhibition, while the polymyxin disc (*2*) has a much smaller zone.

Fig. 5.—Agar plate seeded with Pseudomonas aeruginosa. Small zone of inhibition around the vitreous (*1*); polymyxin disc (*2*) also has a definite ring, while the neomycin disc (*3*) has only a partial sign of sensitivity.

Figure 4

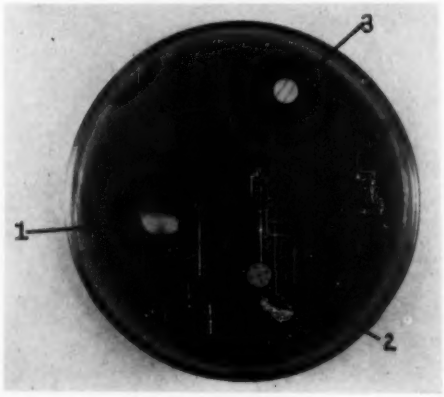
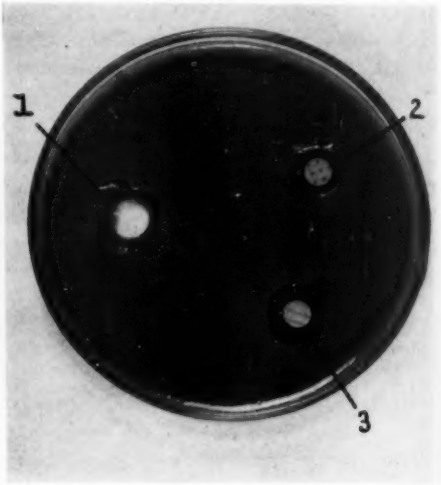


Figure 5



and a small but clear zone on the Pseudomonas plate, are shown in Figures 4 and 5, respectively. These zones of inhibition were still present as long as three weeks later.

Comment

This study actually raised more questions than it answered. It seems safe to say that there is some property in aspirated human vitreous that is antibacterial to all but one of the organisms checked and reported so far. It is also apparent from Reed's work that research along these lines with use of animal vitreous cannot be assumed to be valid for human vitreous.

In spite of the antibacterial effect noted in this study, it is a well-known fact that disastrous infections of the vitreous do occur. It has been suggested that this is due not to the lack of resistance but to an overwhelming number of organisms and a slow response of the defensive mechanisms. We are all familiar, as a parallel situation, with septicemia, and we know that this occurs in the face of known defensive mechanisms. We are also aware of the drug resistance of many organisms. Therefore, vitreous infections in themselves do not mean that no antibacterial quality exists in vitreous. The results of this study emphasize the importance of the identity of the offending organism and the quantity of the contamination in determining whether or not there will be a frank infection.

The questions raised now are the following: 1. What is the factor in vitreous that causes bacterial inhibition or self-sterilization of the vitreous? 2. Is this a substance that is found in the blood and thus enters the vitreous? 3. Is it due to lysozyme or some other enzyme that may be present in the vitreous? 4. What is the chemical and physical nature of this factor? These are only a few of the many questions that are raised by this study. One of the next steps will be the systematic screening of known strains of various organisms. Further work will have to be more quantitative, and the vitreous, both incubated and refrigerated, should be checked for a longer period to see when self-sterilization occurs and whether refrigeration plays a significant role.

Summary and Conclusions

Contamination studies were done with human vitreous to determine if it possessed any self-sterilizing properties and if the method of collecting and storing vitreous for surgical use was adequate to insure sterility. The vitreous used in these experiments was from the Eye Bank store of vitreous and had been treated identically with vials which were to be used surgically.

The number of organisms used in the contamination seemed to be the important factor in obtaining self-sterilization within 48 hours. If fewer than 1500 organisms were injected into the vial containing 2 cc. of vitreous, the refrigerated vitreous was sterile within 48 hours and the incubated was not. If more than this number of organisms was used, neither the refrigerated nor the incubated samples were sterile after 48 hours. This would seem to be a critical level of contamination.

Zones of inhibited growth were noted around pools of vitreous on blood agar plates seeded with Staphylococcus pyogenes var. aureus, Koch-Weeks bacillus, Proteus vulgaris, and Pseudomonas aeruginosa. On all but the Pseudomonas plate the zones of inhibition were larger around the vitreous than around the antibiotic-impregnated discs placed there for comparison.

Isolation of the factor or factors in human vitreous responsible for the inhibited bacterial growth will have to be worked out in future biochemical studies.

The validity of the procedures used at the Eye Bank for the aseptic aspiration and storage of human vitreous for surgical use is confirmed.

210 E. 64th St. (21).

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Metastases of the Retinoblastoma to the Central Nervous System

Advisability of a Combined Intraorbital and Intracranial Removal of the Affected Optic Nerve

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Retinoblastoma is a highly malignant neoplasm which originates from the neuroectodermal elements of the retina. In a proportion of cases, the tumor is congenital and it may be detected during the early months of life by clinical means. However, the commonest time when definitive diagnosis is made is about 2 years of age. The incidence of retinoblastoma was estimated by Weller [1] as 1 in 34,000 births. The main principles of treatment consist of enucleation of the eye followed by radiation or radiotherapy alone. The true rate of complete recovery after institution of treatment is difficult to assess. In many of the published reports the authors do not follow their patients for a sufficient length of time to permit comprehensive evaluation.

We have attempted to review the literature published since 1945 of the documented cases of retinoblastoma that have been adequately followed. The criteria for accepting the reports required that all patients treated were included in the published article and all were followed for at least five years. The results obtained can be seen in the Table. Of the total of 212 patients treated for retinoblastoma 93, or 43.8%, were alive five years after therapy was instituted. The number to survive five years varied with each author from 17.6% to 72%.

The principal purpose of this communication is twofold: (1) to demonstrate the extensiveness of metastases involving exclusively the nervous system in our two consecutive patients, and (2) to analyze the advisibility of a combined surgical treatment of the ocular retinoblastoma, consisting of enucleation of the eye and intracranial resection of the corresponding optic nerve up to the chiasm.

Documented Cases of Retinoblastoma

	Cases, No.	Alive After 5 Yr.
Martin & Reese [2,*]	9	6
Waldman & Shannon [3]	1	1
Reese et. al. [4]	19	12
Fricke et al. [5]	88	40
Stallard [6,*]	29	9
Stallard quotes [6]	17	3
Windeyer, quoted by Stallard [6]	11	8
Verhoeff [7]	1	1
Stallard [8]	36	12
Zimmerman & Ingalls [9]	1	1
Total	212	93 (43.8%)

* It is possible that certain patients might have been included twice in publications of the same authors.

Report of Cases

CASE 1.—This patient was a boy aged 5 years 1 month. The family history was negative for the presence of retinoblastoma. The patient was the second child of young and healthy parents. The pregnancy was normal and full term. The delivery was spontaneous and easy. The birth weight was 7 lb., 7 oz. His early development was normal in all respects until 3 months of age, when retinoblastoma of the left eye was diagnosed. This eye was enucleated, and irradiation was administered to both orbits.

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From the National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service, Department of Health, Education, and Welfare.

Fig. 1 (Case 1).—The patient six weeks before his death. The attitude of decerebrate rigidity is evident.

Fundoscopic examination of the right eye at the age of 7 months disclosed the presence of a small retinoblastoma and incipient glaucoma. Consequently, this eye was also removed and more radiotherapy was given. This was followed by a severe postradiation skin reaction over the temporal portals of irradiation. At the age of 2½ years he was given an additional course of radiotherapy. The over-all total dose received by the patient was slightly over 23,000 r (measured in air).

Except for vision, the child developed satisfactorily in both physical and mental spheres. He walked at 15 months and spoke in sentences at the age of 3 years. He was a pleasant child and showed a great interest in music. His general condition was satisfactory until he was 4½ years old. At this time he began to suffer from general malaise, nausea, and headaches. Examination disclosed an intelligent but irritable child. He demonstrated slight trunkal incoordination and postural dizziness but no other neurological abnormality. Roentgenogram of the skull showed incipient separation of the sutures and a small area of bony erosion at the base of the skull. The cerebrospinal fluid pressure was increased, although it contained normal constituents. It was thought that the patient most likely suffered from intracranial metastases of retinoblastoma. Neither an exploratory craniotomy nor additional radiotherapy was felt advisable, particularly in view of the skin condition and the large amount of irradiation the patient had previously received. The circumference of the skull was measured every two weeks, and it was found to be expanding on the average of about ½ in. every 15 days. The patient continued to vomit and have headaches and gradually became bedridden. Frequent opisthotonic seizures were observed. He also showed progressive weakness and wasting of all extremities of lower motor neuron type, as well as signs of long tract involvement (Fig. 1). Finally he died in a state of decerebrate rigidity about three months after the onset of the terminal illness.

Postmortem examination revealed bronchopneumonia and general emaciation. There was no evidence of metastases outside

Fig. 2 (Case 1).—The chiasm and all cranial nerves are surrounded by numerous neoplastic nodules. The subarachnoid space over the base of the brain and in particular over the cerebellum is invaded by the tumor.

Fig. 3 (Case 1).—The spinal cord and especially the cauda equina are enveloped by numerous neoplastic masses.

brain from the level of the olfactory trigone to the cerebellum (Fig. 2). There was some spreading of small tumor nodules along the Sylvian fissure, but the convexity of the brain was normal. The spinal cord was almost completely enveloped by numerous tumor masses which tended to coalesce, particularly in the region of the cauda equina (Fig. 3). On transverse sectioning of the brain, the ventricular system was found to be moderately dilatated and there was a large tumor mass in the region of the vein

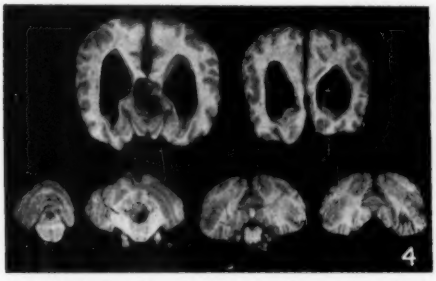


Fig. 4 (Case 1).—Coronal section of the brain discloses a moderate degree of hydrocephalus which resulted from the occlusion of the posterior part of the third ventricle by a large tumor mass.

of the brain, spinal cord, and base of the skull. The brain was large and weighed 1,710 gm. The optic chiasma and all cranial nerves were involved in extensive metastases which formed various-sized nodules and which also infiltrated the subarachnoid space and leptomeninges on the base of the of Galen. This was composed of hemorrhages of various ages, necrotic areas, and neoplastic tissue (Fig. 4).

Histologically the neoplasm consisted of rounded or polygonal cells with scanty cytoplasm. The nuclei were large and stained deeply with hematoxylin. The center of the

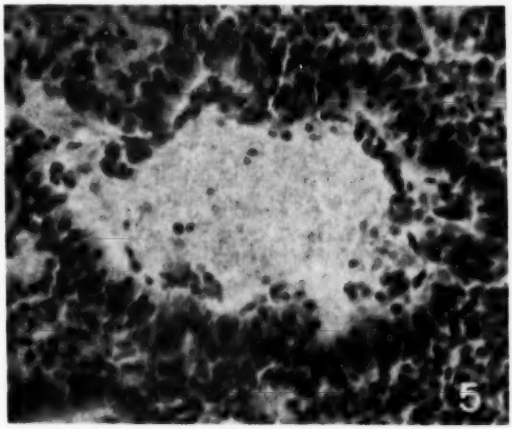


Fig. 5 (Case 1).—Pseudorosette around a small area of necrosis.

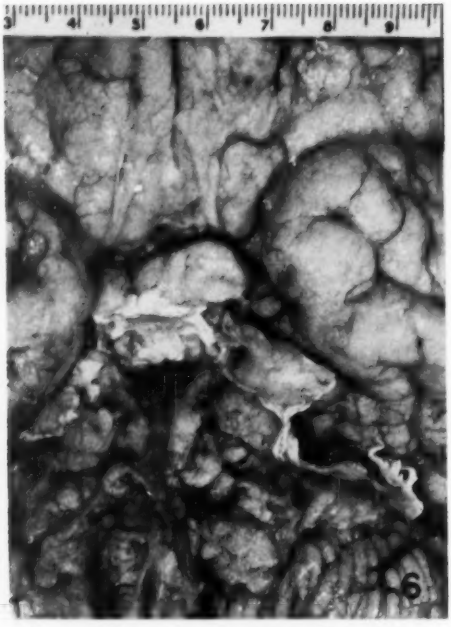


Fig. 6 (Case 2).—The optic chiasm and all cranial nerves are heavily infiltrated and surrounded by the neoplastic tissue.

large tumor nodules showed areas of necrosis and degeneration. In regions of greater viability of the cells, numerous mitotic figures were seen. In general, the cells tended to be arranged in the form of pseudorosettes around necrotic centers (Fig. 5). However, there were also true rosettes present as well as rows of retinoblasts around the blood vessels. At many levels the neoplasm completely surrounded the spinal cord and extended along the arachnoid septa and blood vessels into the nervous parenchyma.

Case 2.—This child was a girl aged 5 years 9 months. The family history was negative for the presence of retinoblastoma. The patient was born at term and developed normally until 7 months of age, when whitish "spots" were noticed in both pupils. After ophthalmologic examination, the diagnosis of bilateral retinoblastoma was made and the right eye was enucleated and radiation was administered to the left eye with apparent improvement. At the age of 3 years the patient developed pain in the left orbit, and this eye also had to be enucleated together with an orbital tumor. Additional series of radiotherapy were administered during the third, fourth, and fifth years of life. The general condition of the patient was fair until 5½ years of age, when she began to complain of pain in the cervical region of her spine and in all extremities. Examination at that time revealed deafness, weakness of facial muscles, slurring of speech, and a generalized weakness. In spite of supplemental cobalt radiation therapy, her course progressed rapidly downhill and she became emaciated and died after a bout of hyperthermia.

Postmortem examination disclosed pyelonephritis, bronchopneumonia, and multiple metastases of retinoblastoma to the brain, spinal cord, and along nerve roots but not

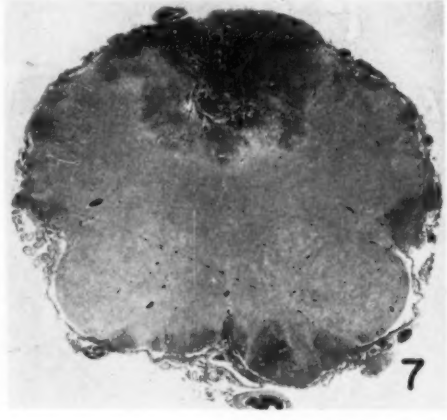


Fig. 7 (Case 2).—The medulla oblongata is invaded by tumor cells which spread from the periphery to the center.

to other body organs. The brain was symmetrical and weighed 1,190 gm. The convolutions were flattened, and there was a moderate degree of herniation of the cerebellar tonsils along the medulla. The leptomeninges over the convexity were normal, but on the base of the brain they were heavily infiltrated by neoplastic masses in the form of rounded and coalescent nodules. The optic chiasm and other cranial nerves were extensively involved and transformed into large cylindrical masses (Fig. 6). The subarachnoid space over the orbital portion of the brain and the basal part of the cerebellum was heavily infiltrated by the neoplasm. Coronal section of the brain did not reveal extension of the tumor to the cerebral cortex, but the basal portions of the cerebellum were invaded. The spinal cord was

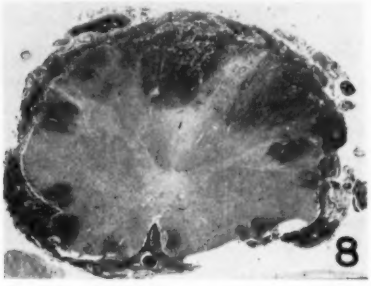


Fig. 8 (Case 2).—The thoracic spinal cord is almost completely surrounded by neoplastic tissue, and about one-half of its cross section is invaded and destroyed.

surrounded by the neoplastic tissue, and numerous nodules extended along the nerve roots into the nervous parenchyma (Figs. 7 and 8).

Histological examination disclosed metastases of neuroblastoma. The predominant arrangement of the tumor cells was in the form of true rosettes or pseudorosettes around the blood vessels or necrotic areas (Fig. 9). However, in the leptomeninges or in the places where the neoplasm infiltrated the nervous tissue, the cell arrangement was less regular (Fig. 10) and invasion was in the form of cords or columns of tumor cells. In the center of large nodules, areas of necrosis, hemorrhages, and calcium

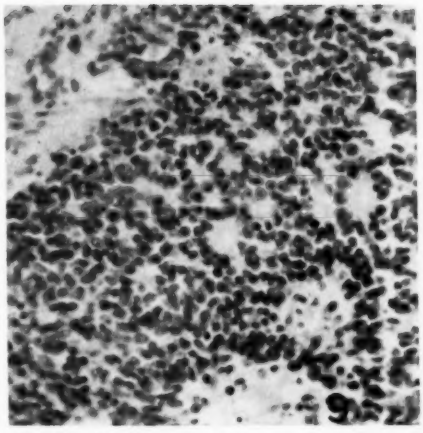


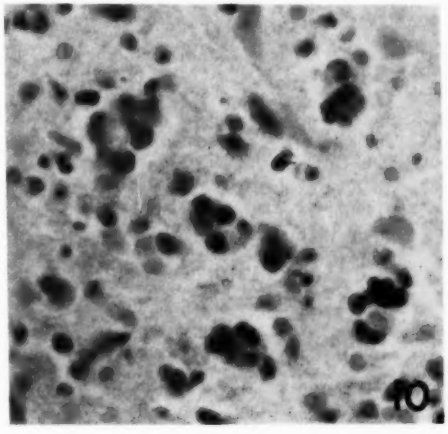
Fig. 9 (Case 2).—Rosettes, pseudorosettes, and mitotic figures.

deposits were present. Mitotic figures were seen with moderate frequency.

Comment

These two children demonstrate an important aspect of retinoblastoma. Following satisfactory treatment the patients survived for 4 years 10 months and 5 years 2 months, respectively. They finally died of metastases involving exclusively the central nervous system. Since it is known that this neoplasm commonly spreads along the neural septa and perivascular spaces, it is perhaps natural that the idea of intracranial removal of the

Fig. 10 (Case 2).—Clusters of neoplastic cells are seen extending toward the gray matter of the spinal cord.



optic nerves up to the chiasma had already occurred in 1922. Jean [10] advocated a combined operation consisting of enucleation of the eye and intracranial resection of the optic nerve. In 1933 he again emphasized the advisability of this approach.[11] In that year Dott and Meighan [12] reported a patient on whom such an operation was first performed. The child showed no signs of recurrence of the tumor two years after the operation, but no subsequent follow-up was given. Rand [13] reported another instance where the combined approach was used; however, in his patient the tumor had already spread to the base of the brain at the time of operation, and the patient died of postoperative complications. Two more cases were reported by Ray and McLean,[14] who have also outlined the intracranial approach in detail. In one child the tumor of the right retina was detected at the age of 7 months. Through a frontotemporal craniotomy the nerve was resected from the optic foramen to the chiasma, and 13 days later the right eye was enucleated. A similar combined operation was used in the second case. Unfortunately, no follow-up reports are available on these patients. The fifth patient with bilateral retinoblastoma who is known to have been treated by the combined operation was reported by Shannon, Jaeger, and Forster.[15] Likewise, the final result is unknown.

It seems remarkable that there was no attempt made to assess the value of such treatment in a larger series of patients with a view to longer follow-up studies and comprehensive analysis of the results. It is worth while to recall that the total length of the optic nerve varies according to the age of the child from about 30 to 50 mm. Of this, approximately 20 to 30 mm. lie intracranially or within the interosseous canal. Figure 11 shows a dissected right optic nerve in an infant 8 weeks old.

Reese [16] found from histological examination of the optic nerves of enucleated eyes with retinoblastoma that in 8.5% the tumor extended beyond the side where the nerve was severed. It has also been pointed out

Fig. 11.—Dissected right optic nerve from the chiasma to the posterior pole of the eye of an 8-week-old infant. Note its length in relation to the metric scale.

by Williams [17] that the absence of the neoplasm in the severed end of the optic nerve of the enucleated eye does not necessarily indicate that all of the tumor has been removed. He states that the extension of the tumor in the optic nerve may not be continuous but that islands of neoplastic cells may be separated by apparently unaffected portions of the nerve.

Unless the lesion is extremely small, the retinoblastoma is seldom treated by radiation alone. Usually surgery is resorted to at some time during the course of the tumor. The operative procedure consists of enucleation of the eye or evisceration of the orbital contents. It would appear logical to assume that, in addition to enucleation, the intracranial excision of an additional 20 to 30 mm. of the corresponding optic nerve should afford a better chance for total removal of the tumor. The risk imposed by the intracranial resection of the optic nerve is minimal when the over-all mortality of this neoplasm is considered.

Summary

Two cases of extensive metastasis of retinoblastoma involving exclusively the nervous system are described. Both patients

had surgical treatment and irradiation. They survived 4 years 10 months and 5 years 2 months, respectively. The literature is reviewed from 1945 until now concerning patients with retinoblastoma who had been adequately followed for five or more years. Of 212 cases it is found that only 43.8% were alive five years after the treatment was started. In view of these findings, it is believed that a serious consideration of the combined operation consisting of intracranial resection of the optic nerve and removal of the affected eye is warranted. This approach has been used in several cases, but, so far, no adequate evaluation of such treatment has been made.

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The Maddox-Rod Phenomenon

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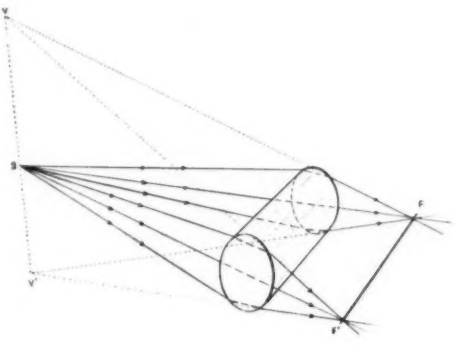
It is an interesting fact that, although the textbooks of refraction and ophthalmic optics describe the use of the Maddox rod in the determination of imbalances of the extraocular muscles, they fail to explain how a cylindrical glass rod can make a light appear drawn out into a line perpendicular to the axis of the rod, and this despite the fact that the explanation is not difficult.

I have been able to find only two explanations in the English literature. The earlier one is by Fincham.[1] He limited his explanation to a much too brief single sentence and then failed to demonstrate it in his accompanying drawing. A reader might well find it impossible to understand Fincham's statement. The second, and much longer, explanation is by Havener and Olesky.[2] Although an accompanying photograph shows an excellent and correct optical model, their description seems obscured to me by a questionable and unnecessary application of the focal interval of Sturm. Therefore, with the hope of being more lucid, I shall offer one more explanation.

The Maddox rod or cylinder has an extremely short focal length, anywhere from 1.5 to 2.5 mm. or more, depending on the diameter of the cylinder or half cylinder that a particular manufacturer has made. In testing for heterophoria, it is worn close to the cornea, usually less than the anterior focal length of the eye. Light rays from a small source (usually first at 20 ft. and then at 14 in.) that pass through such a cylinder are brought to a focus along a line that runs parallel to the axis of the cylinder at about the posterior focal length of the cylinder.

Assume the cylinder to be in the horizontal position. Those rays that pass through it may be thought of as fanning out through innumerable vertical planes which start or intersect in an imaginary vertical line that passes through the light source. In each of these imaginary vertical planes which fan out horizontally from the light source, the light rays also diverge vertically as they approach the cylinder. Upon reaching the cylinder the rays are very sharply bent to a focus and, continuing in their original diverging vertical planes, they pass through the posterior focal line.



This is a schematic three-dimensional sketch. The source of light is at *S*. Assume the Maddox rod to be in a horizontal position. The paths of only six rays of light are shown, three rays in each of two planes which diverge as oblique vertical planes from the light source.

In each of these two planes the rays encounter the cylinder and undergo strong refraction to pass through the posterior focal line *FF'*. They continue in these planes, but they are too sharply divergent to permit the eye to focus them through its vertical meridians.

If these rays are regarded from the aspect of the oblique horizontal planes in which they lie after refraction, the planes which pass through and intersect in the focal line *FF'* and fan out from there, it will be seen that they have undergone no refraction or change of vergence in these planes but only a vertical displacement as by a series of prisms. Since the divergence from the source of light in these obliquely horizontal planes is not great, the corresponding meridians of the eye can refract the rays horizontally to form a point image in each plane or a vertical line from the aggregate of innumerable oblique horizontal planes. These rays appear to come from a virtual line-object, *VV'*, which passes through the source of light, *S*.

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However, the vertical divergence of the rays through the focal line is so great that the dioptric mechanism of the eye (cornea and lens) cannot converge them sufficiently to form an image on the retina of the focal line of the cylinder. However, in the opposite planes—the innumerable oblique horizontal planes that may be thought of as starting or intersecting in the posterior focal line of the cylinder—the divergence of the light rays is very much less (only that resulting from the distance of the light source from the eye). In these planes, where there has been no refraction by the cylinder, the eye easily can focus the rays to form a vertical line on the retina. This line image on the retina then is projected out into space as a line that runs vertically through the source of light. This is illustrated in the accompanying schematic sketch.

Thus, it is evident that the Maddox-rod phenomenon results from the fact that the eye is not able to focus the rays that pass through the cylinder in the same planes in which they have undergone refraction but only in the opposite planes in which the cylinder has not had any refracting effect on the rays.

Multiple Maddox rods, or their equivalents, are made in various ways. Some manufacturers make a series of rods or half rods in parallel, or a series of concave grooves in parallel, or they alternate half cylinders with grooves. For a strongly concave refracting surface (instead of a strongly convex one), the explanation is essentially similar. Upon reaching the concave surface, the rays are sharply diverged as from a virtual focal line in front of the cylinder. Again, in the meridians of refraction, the divergence of the rays is too great for the eye to focus them, but in the opposite planes, where there has been no refraction by the groove, the divergence of the light rays is only that which results from the distance of the light source from the eye, and the focusing mechanism of the eye can form an image on the retina.

30 E. 40th St. (16).

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The Fornix Conformer

A New Device in Reconstruction of the Fornices

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The fornix conformer was devised about four years ago for the smooth reconstruction of conjunctival fornices in cases in which the presence of a seeing eye precludes the use of the standard complete conformer. The previous technique of passing two or three double-armed sutures through the lid obviously was susceptible of improvement.

The device consists of a narrow crescent of methyl methacrylate polymer shaped to fit either the upper or the lower fornix. As depicted in Figure 1, the conformer was cast from a pattern shaped in dental wax. Double holes were drilled with a dental drill to allow the passage of three pairs of double-armed sutures from the conjunctival side. Sutures were tied over pegs on the skin.

In recent cases, a modification was used in positioning peritoneal grafts replacing almost the entire conjunctival surface. The conformer was cut as a segment of a standard plastic orbital conformer, and apertures for sutures were drilled transversely instead of vertically (Fig. 2). The increased vertical width of the device in this type of case served to control the free graft more effectively than the narrower crescent described above.

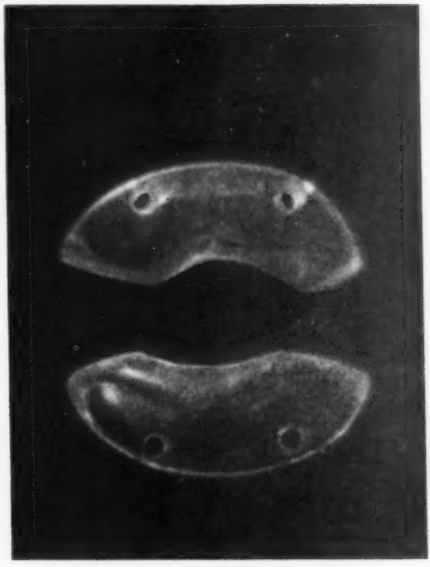

Fig. 2.—Fornix conformer, Type 2.

The method of installation of the fornix conformer to secure a smooth deep fornix is shown in Figure 3.

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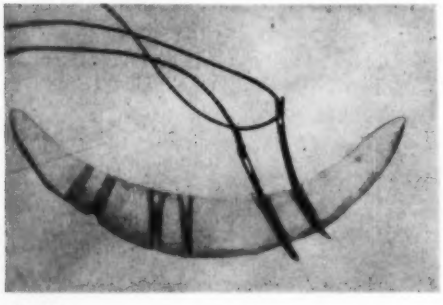
New York Eye and Ear Infirmary; Assistant Plastic Surgeon (Dr. Lubkin) and Consulting Plastic Surgeon (Dr. Hughes).

41 Park Ave. (16).

Fig. 1.—Fornix conformer, lower, Type 1.



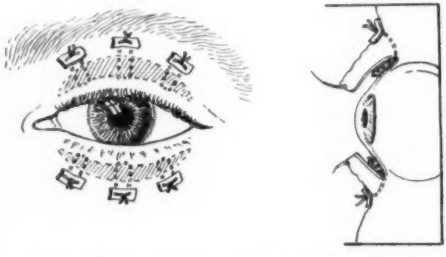


Fig. 3.—Method of installation of conformers.

Cataracts Produced by Dinitrophenol

An Experimental Study

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The first report of a cataract developing in man after the ingestion of dinitrophenol was in 1935.[1] Six years later Horner[2] collected from the literature 177 cases. The cataracts occurred approximately 15 months after the drug was received.[3] Horner,[4] in 1942, stated, "all attempts to produce experimental cataracts in laboratory animals by various and repeated doses of dinitrophenol have been unsuccessful." Bellows,[5] in 1944, also commented on the fact that ordinary laboratory animals do not develop cataracts when dinitrophenol is given. Krause[6] attributed this failure to a difference in the metabolism of the species.

Robbins,[7,8] in 1944, experimentally induced cataracts for the first time in ducklings and chickens by the oral administration of dinitrophenol. He observed a fine gray opacity that progressed to involve most of the anterior portion of the lens. Upon continued feeding the changes in the anterior portion of the lens subsided; however, the opacities in the posterior portion of the lens persisted. Microscopically, vacuolar changes first were present in the anterior portion of the lens and later greater destruction, with cyst-like lesions, occurred in the posterior part of the lens. When lower concentrations of the drug were fed, either the time of development of the opacities was delayed or none occurred. In older chickens the lesion in the anterior portion of the lens usually healed in 6 to 10 days, leaving neither gross nor microscopic changes.

Bettman,[9] in 1946, induced cataracts with dinitrophenol in a special strain of mice. In 1957, Ogino and Yasukura[10] produced cataracts with dinitrophenol in ascorbic acid (vitamin C)-deficient guinea pigs. Cataracts produced by dinitrophenol now have been observed in man,[1,11-19] chickens,[7,20,21] ducks,[7] guinea pigs,[10] and mice[9] but not rats, rabbits, and dogs.[10] Recently we have produced cataracts in chick embryos by injecting dinitrophenol into the yolk sac.[22]

There is considerable discussion as to the pathogenesis of dinitrophenol-induced cataracts. Bellows[5] has stated that all the disturbances produced by dinitrophenol are attributable to its action in accelerating the rate of oxidation. Dinitrophenol leads to an acceleration of oxygen consumption. In tissues where the oxidation is anaerobic it increases the formation of lactic acid.[5] Ronzoni and Ehrenfest[23] also observed that dinitrophenol accelerated the consumption of oxygen and the production of lactic acid in anaerobic metabolism. Krause[6] thought that this drug interfered with glycolysis by deranging the creatine metabolism. Onfray and Dreyfus[24] suggested that the lens opacities may follow liver damage produced by dinitrophenol. In such cases, the lens first becomes dehydrated and then swells. Ogino and Yasukura,[10] after an extensive study of this problem, concluded that the cataractogenic agent in dinitrophenol cataract was 2-amino-*p*-quinonimine. This conclusion seems reasonable according to these investigators

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because the hydroxyl and nitro radicals of dinitrophenol in *p*-position are essential to the production of cataracts. Hessing [25] has suggested that a genetic predisposition plays an important role in the susceptibility to a dinitrophenol cataract.

In view of the increased metabolic rate resulting from dinitrophenol and the implication that an oxygen deficiency may be a factor in the pathogenesis of these cataracts, it is of interest to know that Bellows and Nelson [26] have observed cataracts in anoxic rats. These cataracts persisted for from three-fourths to one hour and gradually regressed. Since the lenticular alterations were transient, it seemed unlikely that they were of an organic nature. Bellows [5] suggested that the change in the lens might be physiochemical and similar to those that follow cold, osmotic changes, etc. Biozzi [27] also observed the occurrence of cataracts in asphyxiated rats, that disappeared when the animals were put into fresh air.

Observations on Chicks Hatched from Eggs Obtained from Hens Fed Dinitrophenol

Seven white Leghorn hens, averaging 1,560 gm. in weight, were given 30 mg. of dinitrophenol in a capsule containing 270 mg. of wheat flour three times each week for eight weeks. A capsule containing only flour was given as the control to eight hens, averaging in weight 1,565 gm. These two groups were kept under identical conditions. Eggs were collected daily and put into an incubator. The lenses of the chicks that hatched were observed at intervals for as long as one month.

The dinitrophenol-treated hens laid 193 eggs during eight weeks of observation, and the controls laid 152 eggs during six weeks. Incubation of the eggs in the latter group was discontinued after the sixth week, since fertility was low. Fertility was high in the dinitrophenol-treated group. One hundred fifty-four chicks were hatched. No lens changes were found in either the experimental or the control group of chicks.

The lenses of the seven hens treated with dinitrophenol were normal at the completion of the experiment. After an interval of several days, these hens were given another 30 mg. capsule of dinitrophenol. The lenses were examined at frequent intervals during the following 24 hr., but no opacities developed. Eight hens of the same breed and weight were given a single capsule containing 30 mg. of dinitrophenol. They were followed for a corresponding interval to determine whether the lenses might have become more resistant to the effects of dinitrophenol during the eight weeks of treatment. No opacities occurred.

Opacities in Lenses of Chickens Given Dinitrophenol Orally

One hundred fourteen chickens of different breeds and varying in age from a few days old to adult were used. Some were followed for as long as four months. The younger chicks were kept in small batteries and the older ones in small pens. A standard commercial ration, cracked corn, and water were available to them at all times. The dinitrophenol was thoroughly mixed with the feed at a level of 0.2% and kept at all times in the food trays. Since the older chickens would not eat the food containing the dinitrophenol, it was mixed with wheat flour and put into gelatin capsules for oral administration. Each capsule contained either 15 or 30 mg. of dinitrophenol and either 270 or 285 mg. of flour. The number of capsules and the frequency with which they were given are recorded in the different experiments. The weight of the chickens was obtained at varying intervals. The eyes were examined with use of reflected light and a dissecting type of microscope.

The opacity in the lens that occurred after the oral administration of dinitrophenol began to develop at the center and progressively increased until the entire lens was involved. The opacity became evident within two to four hours following the oral administration of dinitrophenol. The intensity of the opacity progressively increased, and

Fig. 1 (Chicken 1087).—This 730 gm. bird was given 30 mg. of dinitrophenol orally. Photograph was made 24 hours later and shows a 3+ opacity.

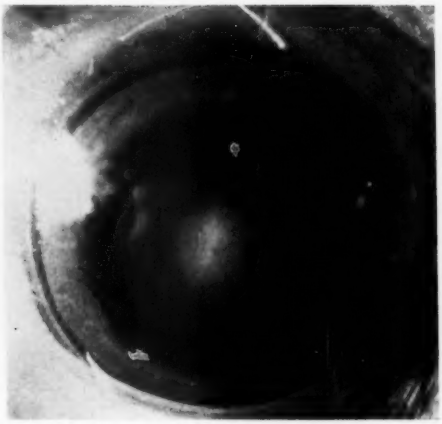

Fig. 2 (Chick C-137).—The lens is milky white. This 2-day-old bird was fed a 0.2% concentration of dinitrophenol for 18 hours immediately preceding the time this photograph was made.

within six to eight hours the entire lens had reached its maximum change. The lens at this time was milky-white (Fig. 1). This opacity then progressively decreased, and after 48 hours the lens was macroscopically normal. Histologic studies were made on the lenses of three chickens 4 days of age fed dinitrophenol for 18 hours immediately preceding the time at which they were killed. Macroscopically the lenses were milky-white (Fig. 2), but no histologic changes were observed (Fig. 3). The lenses from five normal chickens of similar age were used for control (Fig. 4). A chicken 30 days of age developed an opacity while being fed dinitrophenol. The food containing dinitrophenol was discontinued, and the opacity disappeared. Fourteen days later the eyes were removed for histologic study; no lesions were present.

The production of these opacities is influenced by the amount of dinitrophenol given per gram of body weight and by the age of the bird. The maximum degree of lens opacity, 4+, occurred in 19 of 29 chickens, 7 weeks of age and averaging 569 gm., when they were given 30 mg. of dinitrophenol (1 mg/19 gm. of weight). The other 10 birds in this experiment died from the effects of the drug within an interval of six hours.

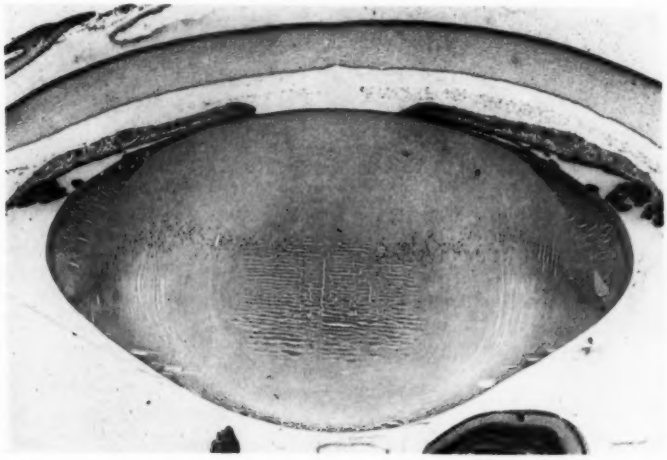

Fig. 3 (Chick C-137).—Microscopic section of lens shown in Figure 2. No histological changes observed in this lens; hematoxylin and eosin; reduced about 10% from $\times$ 27.

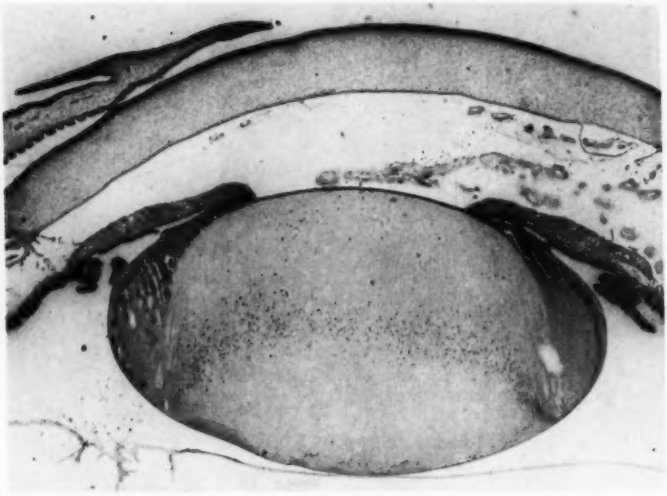

Fig. 4 (Chick 140).—Lens from a normal chick 4 days of age; hematoxylin and eosin; reduced about 10% from × 27.

A second group of four chickens, 10 weeks of age, averaging 1,055 gm., were given 15 mg. of dinitrophenol (1 mg/75 gm. of weight), and only one bird showed a 1+ opacity. Two days later these same chickens were given 30 mg. of dinitrophenol (1 mg/35 gm. of weight) and one showed a 4+ lens opacity; two, a 2+, and one, a 1+.

A third group of 24 chickens, 13 weeks of age, averaging 1,212 gm., was given 30 mg. of dinitrophenol (1 mg/40 gm. of weight) at 4 p. m. on one day, and at 8 a. m. the following morning 21 of the birds had an opacity. There was, however, some variation in the degree of cloudiness of the lenses. Eight showed a 4+; three, a 3+; five, a 1+, and three, no change. The degree of involvement of each lens was approximately the same in any one bird.

In a fourth experiment two chickens, 4 months of age and averaging 1,500 gm., were given 30 mg. of dinitrophenol (1 mg/50 gm. of weight) at 8 a. m. This dose was repeated at 11:30 a. m., and at 4:30 p. m. One bird showed a 2+ opacity and the second remained normal. Within a period of nine hours these two chickens received 90 mg. of dinitrophenol (1 mg/16 gm. of weight), and only one showed a moderate degree of lens opacity.

In a fifth experiment seven adult hens, averaging 1,565 gm., were given 30 mg. of dinitrophenol (1 mg/52 gm. of weight). This dose was repeated in three hours. No lens opacities occurred. Four of the seven hens died within four to six hours after the second dose of dinitrophenol was given.

A second problem in the study of the effect of dinitrophenol on the lens of chickens was to evaluate the effect of multiple doses of dinitrophenol when given at varying intervals. There would be some variation in the weight of the chicks when the second and third doses of dinitrophenol were given, since the birds continued to gain in weight after the first dose of this drug. In one of the experiments, seven chickens, 7 weeks of age, averaging 543 gm., were given 30 mg. of dinitrophenol (1 mg/18 gm. of weight). Each of these seven chickens showed the maximum degree of lens opacity. Four months later the same seven chickens, averaging 825 gm., were given 30 mg. of dinitrophenol (1 mg/27 gm. of weight). Only one chicken showed a 3+ opacity; two showed a 2+; one showed a 1+, and three showed no change whatsoever in the lens.

The lethal effect of dinitrophenol, as would be expected, varies with the age and weight of the bird. One milligram of dini-

trophenol given per 20.7 gm. of weight to chickens 8 weeks of age and averaging 623 gm. in weight resulted in the death of 7 in a group of 14 birds. One milligram of the drug given per 28.9 gm. of weight to 29 chickens 10 weeks of age and averaging 688 gm. did not produce death in any bird. When one milligram of dinitrophenol per 52.1 gm. of weight was given to seven adult hens averaging 1,565 gm. and the dose was repeated three hours later, four of the seven birds died. Death usually occurred two to four hours after the oral administration of the larger doses of dinitrophenol.

Opacities in Turkeys Given Dinitrophenol Orally

Dinitrophenol was given orally to eight turkeys, 2 weeks of age and averaging 217 gm. One of these birds was given a 30 mg. capsule of dinitrophenol, and he developed a 4+ opacity (Fig. 5) within 8 hours and died within 24 hours. A second turkey was given a 30 mg. capsule of dinitrophenol, and death occurred six and one-half hours later. The lenses showed only a 1+ opacity. Six turkeys were given a 15 mg. capsule of dinitrophenol, and five of these developed a 1+ to 3+ opacity. Three of the turkeys died within four to eight hours after the dinitrophenol was given. One turkey was given a 15 mg. capsule of dinitrophenol, and 24 hours later the lens showed a 3+ opacity. This opacity progressively regressed and was completely absent 48 hours after the drug was given.

Fig. 5 (Turkey A).—This 2-week-old bird (215 gm.) was given 30 mg. of dinitrophenol orally. This photograph was made 24 hours later and shows a 4+ opacity.

Degeneration of Lens in Chick Embryos Injected with Dinitrophenol

In a previous study it has been shown that dinitrophenol, when injected into the yolk sac of developing chick embryos, produced degeneration of the lens.[22] In the present study it has been shown that chicks one day of age and older, when fed dinitrophenol, develop only opacities in the lens which spontaneously regress when the drug is discontinued. No histologic changes have been observed in the lenses of baby chicks fed dinitrophenol.

The technique used for the production of degeneration in the lenses of chick embryos given dinitrophenol is the same as that used in a previous study.[22] Dinitrophenol (0.5 ml. [500μg.]) was injected directly into the yolk sac of embryos 8 to 15 days of age. After varying intervals the neck of the embryos was severed and the entire head of the younger embryos was fixed. The eyes were enucleated from the older embryos and chickens. An opening was made into the posterior half of the eyeball before fixation. All eyes were fixed in a 4.0% solution of formaldehyde and embedded in paraffin, and sections were prepared and stained with hematoxylin and eosin. Select sections were stained by Mallory's aniline blue technique.

The percentage of chicks that hatch after the injection of dinitrophenol into the yolk sac is low, and only a few of those have lesions in the lenses. To determine the frequency of this lesion 19 8-day-old embryos were killed four days after the injection of dinitrophenol. Twenty-three embryos, 13 days of age, were used as controls. Histologic sections were made from both lenses from the 42 embryos in these two groups. Five of the embryos given injections of dinitrophenol showed degeneration in the lens. The degree of injury in this group of embryos was much less than has been present in some of the other dinitrophenol-injected embryos.

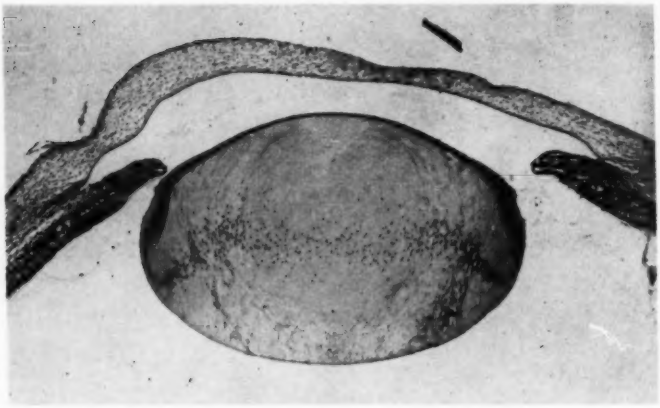

Fig. 6 (E. 245).—This embryo was 8 days of age when 0.5 ml. of dinitrophenol was injected into the yolk sac. Eight hours later the embryo was killed. Degeneration is present; hematoxylin and eosin; reduced about 10% from × 46.

Dinitrophenol was injected into the yolk sac of a second group of 8-day-old embryos. Five embryos were killed on the fourth day, and only two showed degeneration in the lens. Five were killed after six days, and only one showed degeneration in the lens. This experiment was repeated, and 10 embryos were killed 48 hours after another preparation of dinitrophenol was injected into a group of 8-day-old embryos. Seven of these showed degeneration in the lens. Twelve days after the injection of the dinitrophenol nine embryos from the same group were killed, and six of these showed lens degeneration. Usually both of the lenses showed similar degrees of degeneration. However, only two sections were studied from each lens, and a variation in the depth of cutting into the different lenses could account for some of the variations in the same embryo. There is, however, a variation in the amount of degeneration in the lens of different embryos from the same experiment.

Embryos were killed at intervals after the injection of dinitrophenol in order to obtain information referable to the rate of progression of the lesion within the lens. Such data are not too satisfactory, since dinitrophenol does not produce equal damage in each lens of every chick. It is of interest, however, to observe macroscopic degeneration in the lens 90 minutes after the injection of dinitrophenol into an 8-day-old embryo. Histologic evidence of degeneration was present in the lenses of three embryos killed eight hours after injection (Fig. 6). It would seem that if injury does

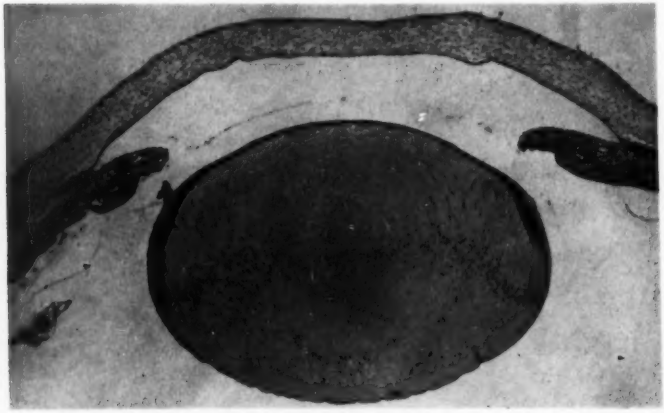

Fig. 7 (E. 247).—This embryo was treated with the same injection as that described in Figure 6. Twenty-four hours later this embryo was killed; hematoxylin and eosin; reduced about 10% from × 46.

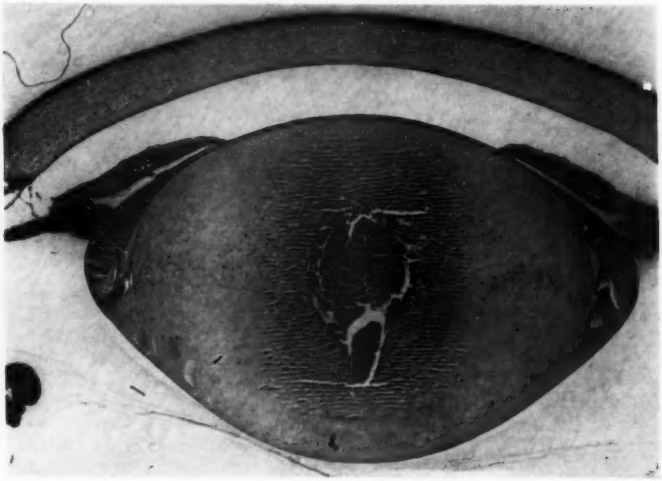

Fig. 8 (C-251).—This embryo was treated with the same injection as that described in Figure 6. Thirteen days later this embryo was killed. Extensive degeneration is present in the center of the lens; hematoxylin and eosin; reduced about 10% from × 46.

occur following the injection of dinitrophenol into the yolk sac of developing embryos, it takes place within a very short time. We have nothing in these experiments to suggest a delay in the reaction in the lens. With elapse of time the degeneration within the lens becomes more marked. Figure 6 shows the change in a lens 8 hours after injection of the dinitrophenol; Figure 7 shows the change in the same group of embryos after 24 hours, and Figure 8 shows the change 13 days later in one group of embryos. In another experiment, dinitrophenol was injected similarly into an 8-day-old embryo and Chicken C-125 hatched. A focal opacity was present in each lens (Fig. 9). This chicken was killed 48 hours later, and the histologic change in the lens is shown in Figure 10.

Fig. 9 (Chick 125).—This embryo was given an injection of dinitrophenol into the yolk sac at 8 days of age. A small opaque area was present in the lens at the time of hatching. Killed 48 hours after hatching.

Comment

Dinitrophenol, as used in this study, did not affect egg production, and the chickens that hatched appeared to be normal. Hens given 30 mg. of dinitrophenol orally three times each week for eight weeks did not show any ill effects. Apparently the effect of this amount of dinitrophenol is not cumulative. Older chickens are less susceptible to the action of dinitrophenol than young birds. Day-old chicks given dinitrophenol in their food in a concentration of 0.2% develop a lens opacity within 12 to 18 hours. These opacities spontaneously regress within 24-48 hours if the dinitrophenol is discontinued immediately after the opacities first develop. A recurrence of the opacity occurs in the same chick if dinitrophenol is repeated. Opacities have been induced and regression has been observed as many as five times in the same chick within a period of four months without

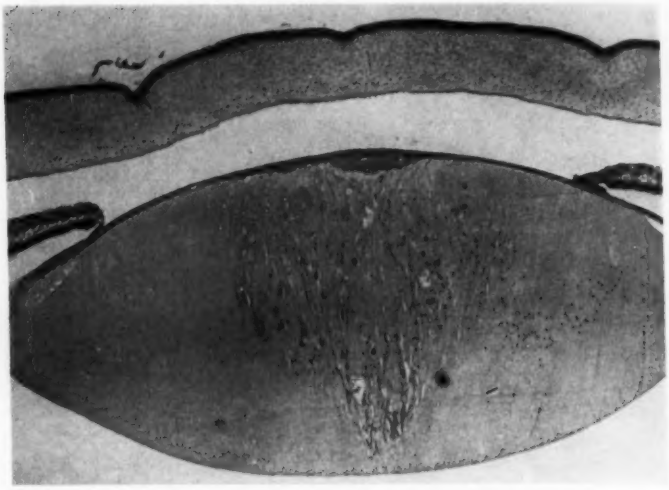

Fig. 10 (Chick 125).—Same lens as shown in Figure 9. The degeneration is present in the area of the center of the lens. Notice the focal area immediately beneath the anterior capsule; hematoxylin and eosin; reduced about 10% from ×45.

macroscopic damage to the lens. Robbins [7] has shown that small amounts of dinitrophenol (0.25%) fed to young chicks over a period of four to five hours results in degeneration of the lens. Buschke [21] has observed the spontaneous regression of dinitrophenol-induced cataracts in chickens.

Degeneration of the lens does occur in embryos given a single injection of dinitrophenol into the yolk sac. Degeneration was present in the lens of one embryo 90 minutes after the injection. Chicks that hatch with lens degeneration may develop normally; however, some are small and weak at the time of hatching. Two chicks with a small lens opacity at the time of hatching have been under observation for six months. No change has been observed in the lens during this time. These birds are to be observed for a longer time.

The earliest histologic change observed is edema of the crystalline lens. In those cases where the degree of injury is minimal, the lens fibers may be swollen and the nuclei show varying degrees of degeneration. Cystic areas varying widely in size were filled with a pink-staining granular material. These areas of degeneration apparently are more likely to develop beneath the anterior capsule in the midportion of the lens. The most extensive lesion we have observed is characterized by liquefication of the greater part of the crystalline lens. The cells in the anterior portion of the lens capsule in focal areas sometimes are vacuolated, pyknotic, and desquamated.

It is of considerable interest to observe the variation in the occurrence of lens degeneration in a group of embryos given a single injection of dinitrophenol. Such variations might be related to the rate of absorption of the dinitrophenol from the yolk sac. Although the injection technique was the same, the site of injection into the yolk sac may have varied unknowingly. The low hatchability of the eggs given injections of dinitrophenol may have been influenced by the type of incubator used, since the percentage also was low for normal eggs. Many of the embryos treated on the 8th day survived until the 17th to the 21st day of incubation. The dinitrophenol-injected embryos appeared to hatch more slowly and frequently were smaller than normal. Several of the chicks given injections of one preparation of dinitrophenol were ataxic at the time of hatching. A study of these will be reported later.

It is of interest to know that the degeneration occurring in the lenses of chick embryos following the injection of dinitrophenol into the yolk sac is morphologically identical with the lesion observed in the lens of vitamin E-deficient turkey embryos.[29]

Of course, necrosis in any tissue may occur by different mechanisms. However, the similarity of the effect of dinitrophenol and a deficiency of vitamin E on the lens may be significant. The variation in the frequency with which lens degeneration occurs after the injection of a specific amount of dinitrophenol into the yolk sac may be related to the vitamin E content of the eggs. It may be that more dinitrophenol is necessary to produce degeneration in the lens when there is a larger amount of vitamin E present.

Summary

Chick embryos may hatch with degeneration of the lens when dinitrophenol is injected into the yolk sac. One-day-old chicks, when given dinitrophenol, develop an opacity of the lens that spontaneously regresses upon removal of the drug. The mechanism by which these changes in the lens are brought about is unknown. It is of interest to find that the degeneration in the chicken lens is similar to that observed in lenses of vitamin E-deficient turkey embryos. The literature is briefly reviewed on dinitrophenol-induced cataracts in man and animals.

Department of Pathology, University of Texas—Medical Branch.

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Elements of Human Extraocular Electromyography

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The recording of potentials from the ocular muscles in man is a new technique which is providing a greater insight into ocular motility and innervation than we have had in the past. While the neurophysiologist considers electromyography a basically simple technique, it is fraught with difficulties in both the recording and the interpretation of the records for others who may not be sophisticated in electrophysiological methods. It is our goal to present the elements of the human electromyography of the extraocular muscles. We hope that this presentation will aid anyone who wishes to take an extraocular electromyogram himself but above all serve as a guide in aiding the reader to interpret and evaluate electromyograms, which are becoming commoner in the ophthalmic literature. Furthermore, this paper will serve as a basis for subsequent publications from this laboratory.

Fig. 1.—Subject supine on gurney in electrically shielded screen room. Eye-movement camera at upper left has no direct connection with electromyography.

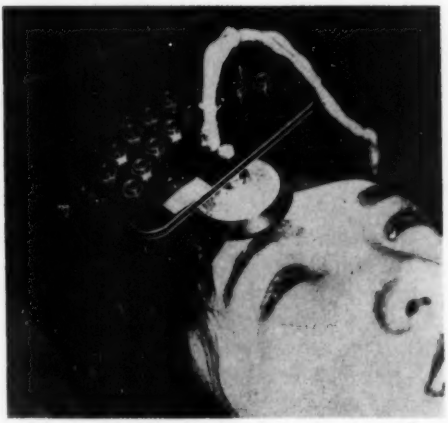

Fig. 2.—Headband, with jacks for leads from electrodes, in place on subject's head.

Fig. 3.—Instillation of drops. Tetracaine or proparacaine (Ophthaine) is used for topical anesthesia; methylcellulose, for prevention of corneal drying, and, sometimes, epinephrine for vasoconstriction.

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From the Department of Ophthalmology, Division of Surgery, Stanford University School of Medicine (Drs. Jampolsky and Tamler). School of Optometry, University of California, Berkeley, Calif. (Dr. Marg).

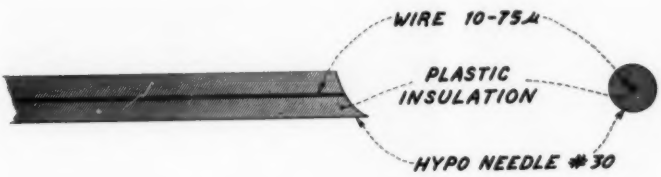


Fig. 4.—Schematic diagram of the muscle electrode, made from a 30-gauge hypodermic needle with an insulated central wire down the lumen.

For those who are going over this ground for the first time and find the terrain rocky, we suggest that the text be overlooked until the illustrations and their captions can be covered without excess effort. The well-trained neurophysiologist, however, will find no new electrophysiological principles in these pages. For those who wish to read more broadly, an extensive selected bibliography is added.

Pictorial Presentation of Ocular Electromyography

Some Details of the Extraocular Electromyograph

As in the apparatus which measures other bioelectric phenomena, such as the electroencephalograph and the electrocardiograph, the electromyograph consists of three basic parts: electrode, amplifier, and display.

The Electrode.—The electrode must be placed in the muscle to record individual units effectively. This dictates use of a needle with an electrically isolated tip. We use a concentric electrode (Adrian and Bronk, 1929) which consists of a 1 in. 30-gauge hypodermic needle in which lies an insulated Nichrome wire which is electrically exposed at the tip.*

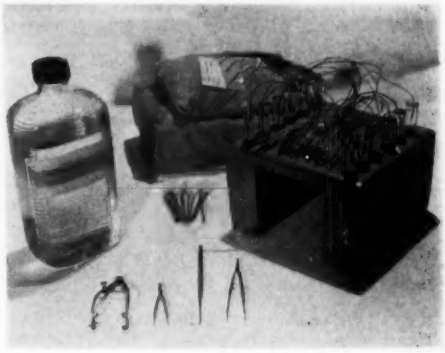


Fig. 5.—Electrodes sterilized in benzalkonium (Zephiran) nitrate. Instruments used are displayed in the foreground.

Fig. 6.—Plain uninsulated needle is inserted in earlobe for electrically grounding the subject.

* Details on the construction of our electrode, block diagrams of the electromyograph and other supplementary material to this article have been deposited as Document No. 5822 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the document number and by remitting $2.50 for photoprints or $1.75 for 35 mm. microfilm. Advance payment is required. Make checks for money orders payable to, Chief, Photoduplication Service, Library of Congress.

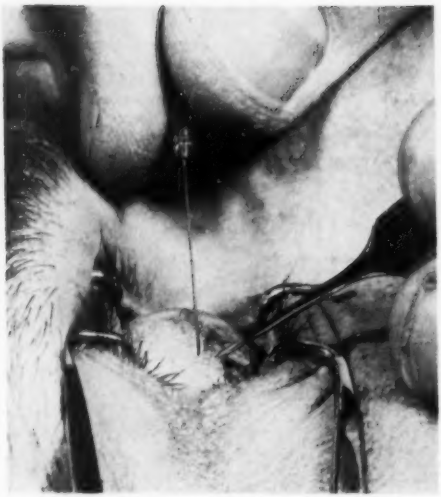


Figure 7

Fig. 7.—The conjunctiva is lifted with a pair of fine forceps, and the needle is inserted through the conjunctiva into the belly of the muscle. A lid speculum is in place. Insertion is guided and judged by the audio response heard from the loudspeaker.

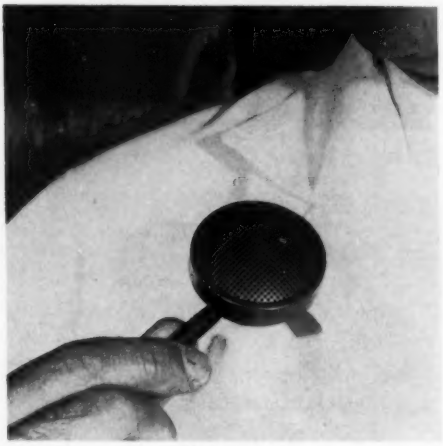


Figure 8

Fig. 8.—Experimental and test procedures are recorded through the lapel microphone worn by the experimenter.

Fig. 9.—Stimulus for fixation is guided by a perimeter or varied through a phorometer. Mirror in background allows simultaneous motion picture recording of eye movements.

Fig. 10.—Thorough shielding of all leads from the screen room is important. In the upper left cable the shielding is obscured by a plastic rubber covering.

Figure 9

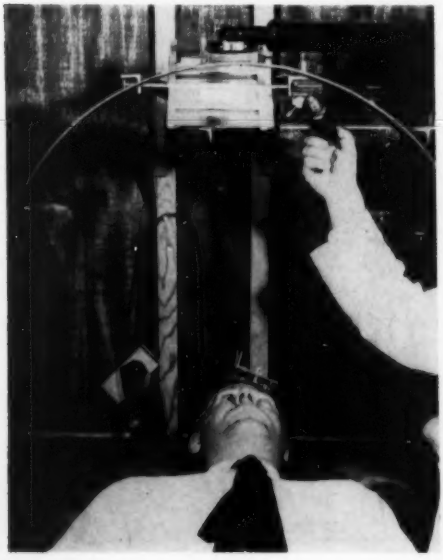
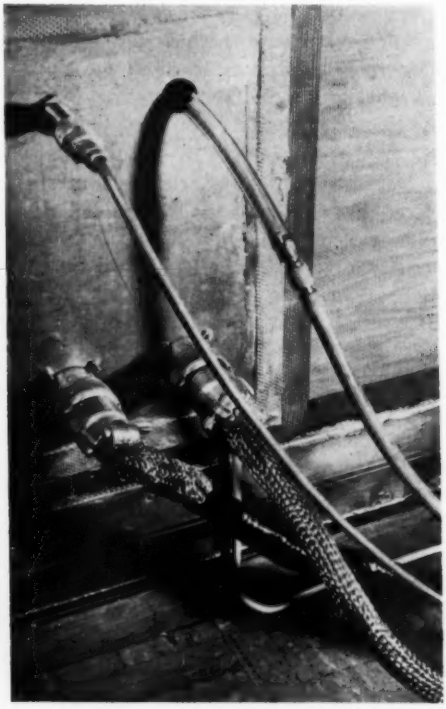


Figure 10



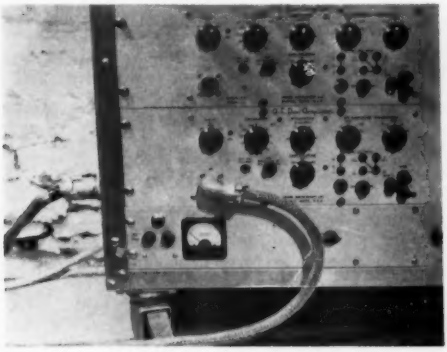


Fig. 11.—Two of a battery of amplifiers which make large potentials out of the small ones from the muscles. A separate amplifier is required for each muscle electrode. The third panel below is a battery charger.

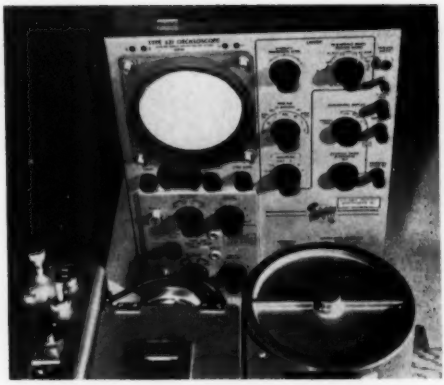


Fig. 12.—The amplified muscle potentials are seen on the cathode-ray oscilloscope. In the foreground is a special camera for a permanent photographic record.

The concentric electrode described is the most convenient to use but difficult to fabricate. Another type, consisting of an insulated entomological pin (as used by Björk and Kugelberg, 1953) is more troublesome, since a second, indifferent electrode must be inserted elsewhere about the eye, usually in the conjunctiva. It has the disadvantage that it is more likely to pick up artifacts and is less durable. Its advantages are lower cost, ease of fabrication, less directional in pick-up, and smaller diameter, which reduces trauma.

Shielding.—Since the potentials which are recorded from the extraocular muscles are exceedingly small (of the order of 50μv. to 100μv.), it is necessary in almost all locations to provide adequate electrical shielding. In practice, this means that the subject must be enclosed in an electrically shielded

Figure 13

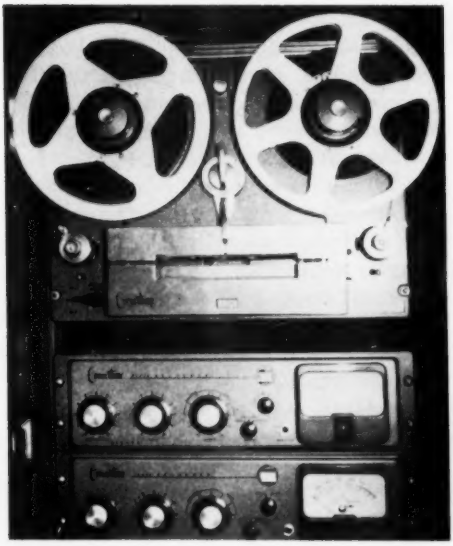


Fig. 13.—A two-channel tape recorder is convenient for recording the experimental procedure from the lapel microphone. The second channel may be used to record an electromyogram. Marking of events can be made on either channel.

Fig. 14.—The complete multichannel electromyograph. Included in this illustration, but not previously mentioned, are the electronic switch for multichannel display; the pulse generator for marking time; two direct-coupled amplifiers for electro-oculography; loudspeakers for listening to the electromyogram, and various switching and coding devices.

Figure 14

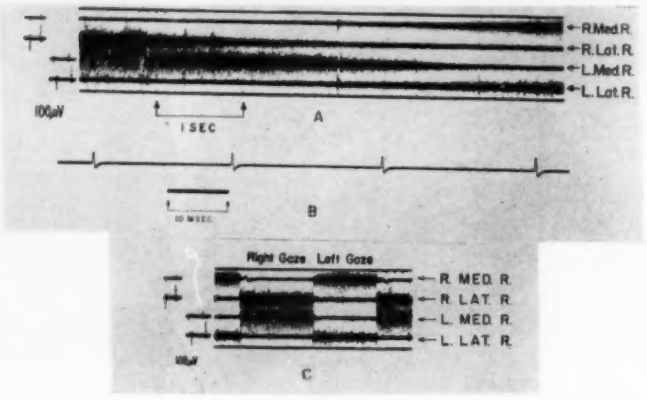


Fig. 15.—*A*, a typical electromyogram showing reciprocal innervation of two pair of opposing muscles of the two eyes. Individual units are not entirely or easily visible at this slow film (sweep) speed. *B*, high film (sweep) speed tracing of a single unit. The shape as well as the size and number of the individual units is seen. An electrode with a 10μ diameter central wire was used, which allows single units to be distinguished even during maximum contraction. *C*, a typical electromyogram at slow film speed, showing saccadic movements of the two eyes.

room, usually made of bronze or copper window screening. The screen room, or Faraday cage, is grounded to a good earth connection at one point, such as a cold water pipe. Without such screening, the electrical noise from light switches, fluorescent lamps, electric motors, television and radio transmitters, and, above all, diathermy machines, which are picked up by the subject's body and the electrodes, may largely mask or completely drown out the electromyogram from the extraocular muscles.

The Amplifier.—A shielded cable carries the electromyogram to an amplifier that makes it large enough to be displayed. The amplifier should have a relatively high impedance input, that is, of the order of 100,000 ohms to 10 megohms, and a frequency response of 2 to 10,000 cps (Buchthal, Guld, and Rosenfalck, 1954), although ordinarily the lower limit we use is 40 cps. It should have a balanced (push-pull) input and sufficient gain or amplification to give an adequate display. It is convenient if the amplifier incorporates a voltage calibration device. The noise level should be very low, that is, not exceeding 7μv. from the top to the bottom peak of the noise with the input leads shorted to ground. There are many such amplifiers available. We use a Grass P5 Preamplifier.

The Display.—The electromyogram can be displayed in two ways, visually and aurally. The auditory display is provided by a loudspeaker from which the electrical activity can be readily heard. In fact, it is far easier to hear an electromyogram than it is to see one, and the placement of electrodes is always done under auditory guidance. For permanent and quantitative records, however, a visual trace is preferable. Therefore, the amplifier is fed into a cathode-ray oscilloscope as well as a loudspeaker. At this point, the question may arise, "Why can I not use my pen-writing electroencephalograph for this work?" The answer lies in the speed of response. Pen-writing instruments usually cannot respond to frequencies greater than 100 cps because of their inertia, whereas the electrical activity recorded from the eye muscles is in the form of spikes which have a duration equivalent to about a thousand cycles per second. Hence, only relatively crude patterns of the response can be obtained from a pen-writer, and the individual units would be largely lost or distorted.

The cathode-ray oscilloscope may be photographed by a camera and, for any useful length of record, it is necessary to have a camera in which the film travels at a constant velocity, a feature of the so-called oscilloscope record camera. Thus, a signal from the muscle moves the oscilloscope beam vertically while simultaneously the film is traveling across the face of the dis-

play tube horizontally, providing a time base or sweep. We use a Grass oscilloscope record camera which has been modified to give a maximum film speed of 2 meters per second.

A cathode-ray oscilloscope is more versatile if it has two beams or tracings instead of one. We use a Tektronix Type 531 dual-trace oscilloscope, although for some types of recording a dual-beam oscilloscope, such as made by DuMont, Tektronix and Electronic Tube Corporation, may be preferable.

Generally, in order to provide more than two channels, it is necessary to have an auxiliary electronic switch which will chop the beam into a series of traces. For this purpose, we have a Burroughs Beamplexer, which can provide as many as 10 channels on one oscilloscope display. A separate electrode and amplifier is required for each recording channel.

An integrator can make the response from a muscle easier to visualize. There are several versions of electronic integrators which need not be discussed here. Suffice it to say that, in general, an integrator takes the potentials from the muscle and adds them with respect to time. The integrated trace would soon run off the face of the oscilloscope were it not, after a certain preset time, returned to baseline. The lower trace in Figure 17 is the integrated activity of the direct trace above it, the slope indicating the rate of activity. It is worth keeping in mind that noise, blinks, and other artifacts are nicely integrated concomitantly with unit activity. This can make such an impressive display misleading.

It is helpful to have a two-channel magnetic tape recorder which can simultaneously record (by means of the lapel microphone worn by the experimenter) information about the test as it is being performed and, at the same time, record any given channel of the electromyogram. The tape-recorded electromyogram, single or multichannel, can be kept as a permanent record and may be played back at a later time through the oscilloscope and photographed at any desired film speed, subject of course, to the frequency limitation of the tape recorder. A marker indicating the instant of various stimulus or response events can be recorded on either channel. We use a common telephone dial, which provides a marking code of 1 to 10 pulses as dialed.

Various miscellaneous stimulus equipment, such as a perimeter arc and a phorometer, is used, but requires no special description.

Unit Activity

An electrode in a muscle may record from a single unit which is recognized by its rhythmicity and its relatively constant size and shape. This unit is commonly thought to be a *motor unit*, that is, a small group of muscle fibers which fire or contract as a unit because they are innervated by the same nerve fiber. However, the size of the response of the individual motor fibers which summate or give a unit response is largely dependent on the distance to the electrode. Therefore, if the individual fibers are spread out spatially, some fibers will contribute to a large degree to the response whereas others will contribute little, if at all (Buchthal, Guld, and Rosenfalck, 1957; Krnjevic and Miledi, 1958). Professor Buchthal and his colleagues have recently suggested the term "sub-unit" for the group of fibers that are recorded in unit activity. It should be stressed that the sub-unit concept has been applied to skeletal limb muscles and is not necessarily applicable to extraocular muscles, where the ratio of motor fibers to nerve fibers is very low, probably a mean of 7:1. Nevertheless, until we know more about the histophysiology of the extraocular muscles, it is perhaps better to avoid speaking of the recording of motor units, since we may be picking up sub-units.

There is good evidence from skeletal muscles of the frog and cat that some muscle fibers are multiply innervated (Hunt and Kuffler, 1954). As yet there is no indication of this polyneuronal innervation in oculorotary muscles.

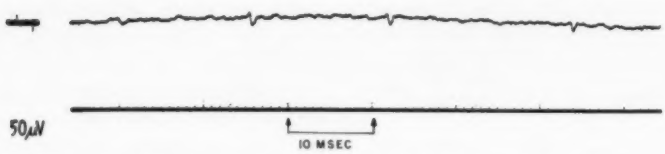


Fig. 16.—Recording from a paralyzed left lateral rectus muscle in extreme right gaze. These units are assumed to be fibrillation potentials because they are small, nonrhythmic, and not correlated with the position of the eye.

In fibrillation, small nonrhythmic spike potentials are seen some weeks after denervation. There is direct evidence that these spikes are from single muscle fibers (Nicholls, 1956; Li, Shy, and Wells, 1957) which fire without regard to attempted voluntary activity. Potentials from a paralyzed oculorotary muscle are seen in Figure 16.

Gradation of muscular contraction is accomplished in two ways. First, by a change of *frequency* of the individual motor units and, second, by the number of motor units active. As a larger number of motor units become active, they are said to be *recruited*. In general, both mechanisms are increased at the same time. There is some evidence of gradation by change of the number of active muscle fibers within single motor units, but the evidence is not yet very clear (Norris and Gasteiger, 1955).

When a single unit responds, we have a *simple pattern* as shown at the very beginning of Figure 17. If more units respond, but still the response is not so great that the individual units are masked, the picture is called a *mixed pattern*, shown toward the middle of the first line in Figure 17. Finally, if the response is so great that the individual units cover one another so that they cannot be individually resolved, the result is called an *interference pattern*, as seen in the third line of Figure 17. An interference pattern makes it generally impossible to determine the frequency response of single units at maximum degrees of contraction without special techniques.

It is believed that the frequency of some of the ocular muscle units reaches values as high as 175 spikes per second or more, but it is difficult to be certain, partly because of the interference pattern (Björk and Kugelberg, 1953; Reid, 1949; Gordon, 1951; Breinin, 1957) and partly because the wave form has not been examined to eliminate the possibility of synchrony of more than one unit giving an erroneous value.

As implied earlier, the amplitude or voltage of the response is largely dependent upon the distance of the electrode from the

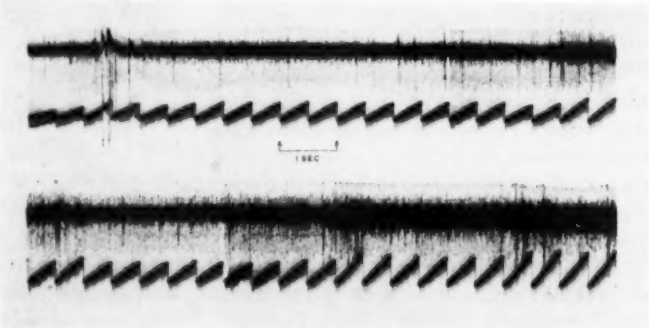


Fig. 17.—Upper tracing shows the activity of the right medial rectus from extreme relaxation to extreme contraction. A single unit pattern can be seen at the beginning of the record which blends into a mixed pattern and ultimately into an interference pattern, above which some units can be distinguished. The lower tracing is that of the upper tracing after it has been put through an electronic integrator which resets itself (returns to baseline) every half second. Note how the slope of these segments of the tracing increases as the muscle contracts.

active fibers. It is also dependent upon the size of the fibers, and therefore the response in limb muscles is many times greater than that of the extraocular muscles.

At times, instead of the diphasic response commonly found in extraocular muscles (Fig. 15*B*), there are four or more phases, or a polyphasic response. They are very rare in the extraocular muscles and are generally considered a sign of recovery from denervation, presumably because the nerve fibers have regenerated in a fashion not favorable for good synchronization of the response of the individual muscle fibers. In the past, it has generally been considered sufficient to identify a single motor unit as a train of uniform action potential spikes on a relatively smooth baseline. However, it is desirable that identification of a single motor unit be more complete, that is, not only that its frequency and its height be identified, but also its wave form. A relatively fast movement of the film or sweep speed is required for display of the wave form, as seen in Figure 15*B*. Notice that the wave forms are essentially all alike. Hence, it is reassuring to examine the wave form before assuming that a rhythmic series of uniform amplitude spikes arises from a single motor unit.†

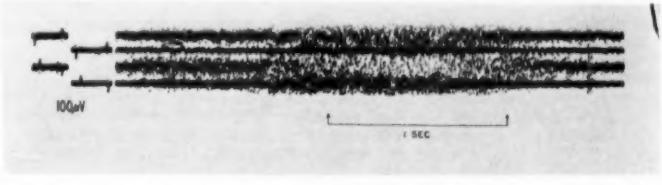
† No direct information can be obtained by the usual extracellular myographic technique about muscle spindles or intrafusal fibers. The small motor nerve system (γ-efferents) to the muscle spindle is well established (Granit, 1955) and recently has been exquisitely demonstrated physiologically in the extraocular muscles of the goat (Cooper and Daniel, 1957). However, any further discussion of this system is outside the scope of this paper.

A serious question arises in using electromyography as an indication of the total activity of a muscle. Is the response, recorded from a circumscribed volume (probably less than 1 mm. in diameter) representative of the activity of the muscle as a whole? In general, this seems to be true, although where there are units of lower threshold they may show activity sooner in a contracting muscle than recordings from other areas where higher threshold units may be found. This is seen in Figure 18, where we have multiple insertions in the same muscle. Upon contraction of the muscle, which presumably is contracting as a whole, there is activity recorded from one electrode before another. Hence, minor time differences during following movements between the recordings of different eye muscles can be misleading on this basis. Furthermore, the eye movement cannot be less than about eight degrees to demonstrate a perceptible change in the electromyogram even with good insertion.

Ocular Electromyography and Muscle Tension

There is no good direct evidence that the electromyogram of the extraocular muscles is directly proportional to the muscle tension. It has been found in limb muscles that there is a direct relationship between the integrated electrical activity and the tension of muscles in isometric contraction (Lippold, 1952; Inman et al., 1952; Bigland and Lippold, 1954; Edwards and Lippold, 1956), but the oculorotary muscles ordinarily do not contract without changing their length under normal conditions. The

Fig. 18.—Three electrodes in the same medial rectus muscle. Note that the activity appears to start in one trace earlier than in the others. When all traces are above threshold, the activity appears proportional in all channels. Hence the higher threshold units appear to lag behind the lower threshold ones but do not in actuality.



common, tacitly accepted, notion that the electrical activity of ocular muscles is a measure of isotonic muscle contraction is not unreasonable but is still merely an assumption.

Interpretation of Events

At a moderate or slow film (sweep) speed, a firing of a single unit results in a spike. This impulse appears on the baseline of the electromyogram, as seen in Figure 15*B*. If several units are being recorded, they will appear as separate impulses unless two or more happen to fire simultaneously. In this case, they will summate, or show the total of their individual amplitudes. It is usually easy to see with fast sweep speed that summation has occurred, because the summated wave form thus exhibited will show tell-tale notches or humps where the units have their individual maxima or minima. Regardless of whether summation occurs or not, however, the trace will return to the baseline within a few milliseconds.

If the amplifier has a long time constant, that is, if it can respond to relatively low frequencies, of the order of 1 cps, then slow potential changes which may be picked up in the electrode will result in a relatively slow drift of the baseline. This slow drift should not be interpreted as potentials resulting from firing of individual units. In fact, it can be eliminated by turning a switch and shortening the time constant of the amplifier, or, in other words, reducing the low frequency sensitivity. In Figure 19 are shown a series of simulated "spikes" in the form of square waves of 1,000 cps. In the upper trace of Figure 19*A*, we see a slow potential drift which is superimposed on the square wave spikes. Note that the simulated spikes show up as clearly as ever, but the baseline is displaced downward from the level of the drawn-in dashed line. In the lower trace of Figure 19*A* is the same signal which has been sent through the usual capacity-coupled amplifier used in electromyography. It is obvious that the simulated spikes appear as clearly as in the original tracing but that the baseline returns more quickly to the normal level, despite the original signal traced above. In Figure 19*B*, the upper trace is the same original signal. In the lower trace, the time constant is shortened and the slow potential drift returns to the baseline much more quickly. The time constant may be shortened further to eliminate almost entirely these unwanted drifts. An actual slow drift can be seen at the beginning of Figure 17 as a sudden baseline shift. It is over quickly because of our short time constant. We use a lower frequency limit of about 40 cps, which makes clearer records without being misleading. The sacrifice of these lower frequencies in the wave forms of single units does not seem to be of significance.

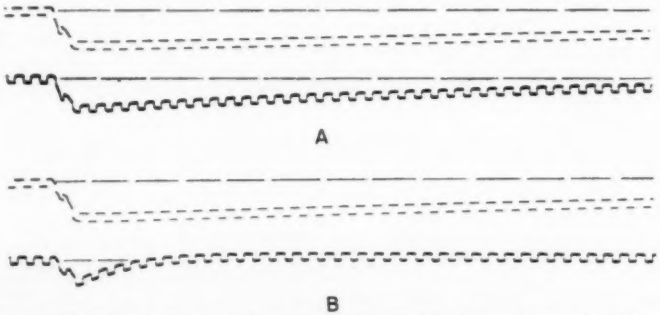


Fig. 19.—Simulated square wave "spikes" at 1,000 cps with superimposed slow potential demonstrating the effect of the amplifier time constant (low frequency response) on the recording of muscle units. *A*, upper tracing shows square wave signal simulating muscle spikes with superimposed slow potential which slowly returns toward dashed baseline. Lower tracing shows the above signal after it has been put through the usual capacity-resistance coupled (A. C.) amplifier. Note that the square wave simulated spikes are seen essentially undistorted whereas the return of the slow potential to baseline is faster than in the original signal. *B*, the same as *A*, except that a switch has been turned on the amplifier which shortens the time constant (raises the low frequency response.) The unwanted slow potential is now largely eliminated.

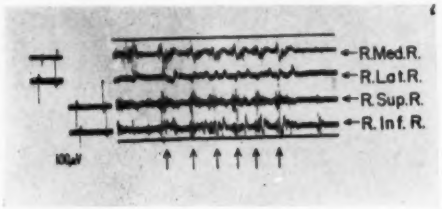


Fig. 20.—The vertical arrows point to the electrical records of the four recti muscles of the right eye during blinks. These artifacts are usually seen simultaneously on all channels.

A thin baseline with adequate amplification is desirable. If the baseline is thick or uneven in relation to the units recorded, then the equipment or location is noisy or else the insertion is poor. It is not a good practice to reduce the gain or amplication to show a better baseline, because in so doing electrical activity of the muscles is difficult to see and analyze.

Often, when the needle is touched by the lid one sees movement of the baseline. A high-speed recording will show that this movement is not characteristic of motor unit activity, and it is usually possible to make this distinction for blinks at lower sweep speed, as is apparent in Figure 20.

On occasion the electrode moves although there is evidence that little or no movement occurs. Specifically, a single unit can be recorded in a given eye position or degree of muscular contraction. After repeated excursions of the eye one can return to the threshold of this unit in what appears to be the same eye position as before. On other occasions, in returning the eye to the same position one does not find the same unit there unless the eye goes beyond this position and returns to it. This can be done repeatedly and indicates that if there is electrode movement here it must be a regular uniform and repeatable one.

It is obvious that when an eye moves the movement is a result of the balanced oculorotary muscular contraction. The electrical unit activity indicates the contraction but not the function of the muscle. For example, the contraction of an oblique muscle may be clearly recorded, but the electromyogram itself gives no hint as to the action, be it elevation or depression, abduction or adduction, intorsion or extorsion.

Advantages of Multiple-Channel Recording

It is useful to have available four or more channels for the recording of the extraocular electromyogram. If a blink should occur, it usually registers on all channels, which makes it easy to distinguish (Fig. 20). In general, distinctive activity by a single muscle stands out more clearly from artifacts during multiple recording.

Instances of coactivity or cocontraction can readily be measured by multiple channels, whereas a single or even a dual-channel apparatus does not give a complete picture. Furthermore, binocular function can be more directly and readily measured. In other words, the interrelations of the four or more muscles are directly seen by the use of multiple channels. Steadiness and maintenance of fixation can thus be readily monitored.

Clinical Value of Ocular Electromyography

Human extraocular electromyography is an important research tool but is of limited clinical value. If there is, at present, a practical usefulness of the technique, it lies in neuro-ophthalmological diagnosis and prognosis.

The selection of patients must be made with care. Generally, children cannot be examined and the personality of adults must be such that they are willing to undergo what to most persons is a somewhat frightening and not entirely painless procedure. Furthermore, elderly patients occasionally get subconjunctival hemorrhages that are cosmetically distressing.

Usually, limitation of eye movement by paralysis, paresis, or mechanical restriction can be diagnosed by clinical means such as observation of eye movements and the forced duction test under general anesthesia. Electromyography only confirms these findings. Therefore, electromyograms are, generally speaking, neither necessary nor helpful in usual practical motility prob-

lems. One cannot distinguish overactivity from underactivity, because the amplitude of the tracing is largely dependent upon the insertion. A moderate or severe paresis or paralysis which can be observed on the oscilloscope is obvious without the aid of electrical techniques.

Niles Roth, A.B., M.D., designed and constructed the electrodes; William Houweling and Bob Markevitch, B.S., M.S., constructed, maintained, and operated the electronic gear and designed the integrator, and Wilmer Renner did the photography.

Stanford University Hospital, Clay and Webster Sts. (15).

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An Electromyographic Study of Coactivity of Human Extraocular Muscles in Following Movements

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Cocontraction is defined as the simultaneous increased contraction of extraocular muscles which are normally antagonistic in their primary field of action. It has been hypothesized that cocontraction occurs when the eye moves from its primary position to any secondary or tertiary position.[1] According to this hypothesis, as the lateral rectus abducts an eye, the vertical recti as well as the obliques cocontract to steady the eye in its horizontal path. At the same time, the cocontraction prevents undue torsion of the globe and helps maintain abduction as the lateral rectus loses its mechanical advantage as the movement progresses. The same reasoning would apply to adduction, supraduction, and infraduction. It is the purpose of this paper to report the results of testing this hypothesis by multiple-channel electromyography.

The steadying effect and reinforcement of eye movement by cocontraction of auxiliary muscles* was postulated as early as 1897 by Duane.[2] By constructing muscle planes and moments of rotation, Verrijp[3] shows the effect of auxiliary muscles in various movements. He believes that muscles other than the prime mover and its antagonist steady the movement and keep the vertical axis from torting. Krewson[4] calculated mathematically the action of all the extraocular muscles in various positions of horizontal gaze by a method of vector analysis. According to this analysis, the vertical recti and obliques are in a position to contribute to internal and external rotation of the eye by cocontracting during horizontal movements. This contribution is greater or lesser depending on the horizontal position of the eye at the time of cocontraction. Gordon[5] cut the vertical recti and found adduction diminished in the immediate postoperative period. After a number of days, full adduction returned, which Gordon interpreted as indicating reattachment of the vertical recti, so that they again could aid in accomplishing normal maximum internal rotation. It is possible, however, that the return of full adduction signified recovery from post operative reaction. Swan[6] studied the horizontal effect of vertically acting muscles when both the medial and lateral rectus muscles were tenotomized in humans under topical cocaine and subconjunctival procaine anesthesia. He found that the vertical muscles had adductive force limited to a few degrees when movement was initiated from the primary position. One of us (A. J.) found that under topical anesthesia only at least half the normal amplitude of adduction and abduction was still available when the medial and lateral rectus muscles and attachments were cut on the operating table. Chamberlain[7] found in the rhesus monkey that the vertical recti and the obliques are of very minor importance in horizontal rotation so long as the primary rotators (horizontal) are intact.

Multiple-channel electromyography affords a more direct method of testing the

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From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine (Drs. Tamler and Jampolsky), and School of Optometry, University of California, Berkeley, Calif. (Dr. Marg).

* By auxiliary muscles, we mean those extraocular muscles other than the prime mover (agonist) and its direct antagonist.

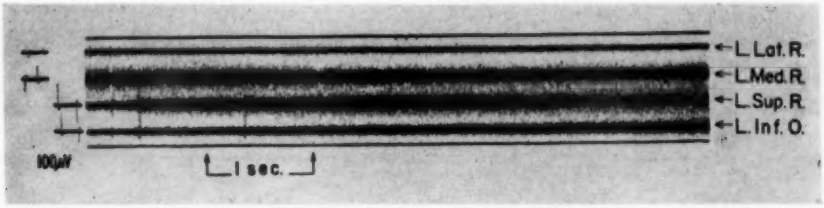


Fig. 1.—Up gaze in sagittal plane of left eye. In all Figures the top line is the signal marker, the bottom line is the time marker, and calibration is at the left. Note no obvious change in horizontal recti.

above hypothesis. We can record the electrical activity of four extraocular muscles simultaneously. The details of the technique have been previously reported.[8] Over the past two years, the findings in scores of patients have been recorded. This paper will deal with electrical coactivity in horizontal and vertical following movements in the plane of the primary position. Although it is widely believed that the recorded electrical activity is correlated with muscle contraction, we prefer to use the term "electrical coactivity," because this is actually what we are measuring. All movements shown were approximately 50 degrees in amplitude. Following movements were stimulated by moving a target along a perimeter arc in the desired direction. The target was held approximately 75 cm. from the eyes.

A. Up gaze. In Figure 1 there is movement of the left eye straight upward in the sagittal plane. There is increasing electrical activity of the two vertical movers, the superior rectus and the inferior oblique, but no obvious change in the recording of the activity of the lateral and medial rectus muscles.

B. Down gaze. Figure 2 is the electromyogram of a downward movement of the left eye in the sagittal plane. The superior rectus and inferior oblique are progressively inhibited. The lateral and medial rectus show no measurable change.

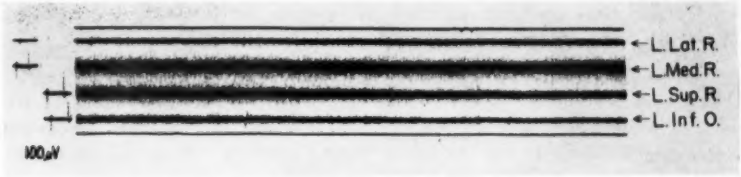
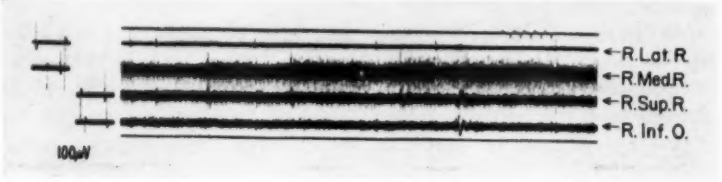


Fig. 2.—Down gaze in sagittal plane of left eye. No measurable change in horizontal recti.

C. Adduction. Figure 3 is the multiple-channel electromyogram of a right eye moving to the left. The first recording is the result of a poor insertion in the right lateral rectus and should be disregarded. There is increasing activity of the right medial rectus

Fig. 3.—Right eye moving to left in horizontal plane. Right lateral rectus not recording, because of poor insertion. No noticeable change in right superior rectus and right inferior oblique.



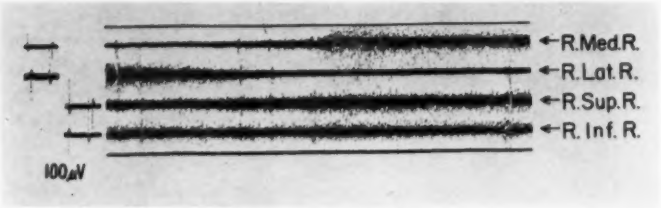


Fig. 4.—Adduction of right eye in horizontal plane. Note slight increased coactivity of vertical recti.

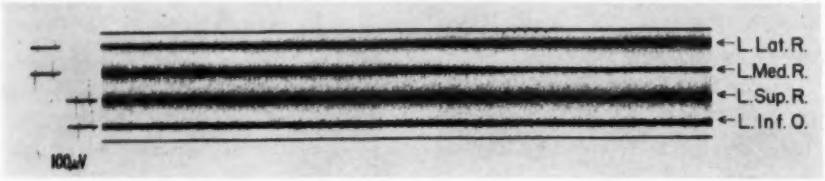


Fig. 5.—Abduction of left eye in horizontal plane. No apparent change in left superior rectus and left inferior oblique.

as the eye proceeds nasalward. The right superior rectus and the right inferior oblique show no noticeable change with adduction.

The absence of coactivity was a general finding. Occasionally the tracings did suggest possible coactivity. For example, in Figure 4 we see a slight increase in activity of the superior and inferior rectus muscles as the right eye is adducted. The right medial and lateral rectus muscles are reciprocally innervated as the right eye moves to the left.

D. Abduction. In Figure 5 the left eye is turning outward. The left lateral rectus and the left medial rectus are reciprocally innervated. The left superior rectus and the left inferior oblique show no apparent change in activity during this movement.

Comment

It appears that there is little or no increased coactivity of auxiliary extraocular muscles in adduction, abduction, supra-aduction, and infraduction during slow, vertical, and horizontal following movements in planes through the primary position. This does not necessarily mean that they do not contribute to the movement. As indicated earlier,[3,4] the effect of muscle activity on eye movement depends upon the position of the eye at that moment. Hence, the primary position innervational tonus of the auxiliary muscles, which does not apparently change during these movements, may indeed contribute to the movement after the eye has gone a certain distance. For example, in Figure 5 the left superior rectus, although showing no change, may be contributing to the abduction of the left eye after the left eye has gone outward more than 23 degrees, and the left lateral rectus is losing its abducting power. Also, the primary position tonus may be all that is necessary to steady the eye and prevent torsion during the movement. In other words, we can only deduce muscle contraction with certainty from the electrical activity of a muscle, but not necessarily the function of the muscle at that moment.

One can therefore say that normal muscle activity as found in the primary position is present in the auxiliary muscles during this movement but that systematic changes in coactivity do not generally occur. We are therefore in basic agreement with Breinin's conclusion regarding the same problem.[9] Adler[10] found slight increased electrical activity in the lateral rectus in straight up and down gaze of an eye, just as we found in the vertical recti (Fig. 4). Occasionally, one does find barely perceptible changes in the traces of the auxiliary muscles during such movements. These changes, when visible, have no systematic pattern and therefore

are not consistent with the cocontraction hypothesis, which would require systematic changes with a given direction of movement.

Generally speaking, we cannot detect the change in electrical activity corresponding to a slow movement of an eye of less than 8 degrees. This could limit our conclusions to the sensitivity of this system. However, since the changes that are occasionally found show no systematic pattern, there appears to be no such limitation on our conclusions.

Summary

Multichannel electromyography on human extraocular muscles demonstrates little or no increased coactivity of auxiliary muscles during slow vertical and horizontal following movements in planes through the primary position.

Assistance was contributed by electronics engineers William Houweling, John Williams, and Bob Markewitch. Technical assistance was given by Niles Roth, A.B., M.O., and photography was by Wilmer Renner.

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Infratemporal Subdural Hematoma as a Cause of Exophthalmos

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In the voluminous literature on subdural hematoma, a characteristic deformity of the skull produced by the lesion when located in the middle cranial fossa of one side was described first by Davidoff and Dyke [1] and later by Bull.[2] Although the deformity encroaches on the orbit and reduces its capacity and must influence the position of the eyeball, exophthalmos was seldom mentioned in the reported clinical histories. It is most probable that unilateral exophthalmos of some degree existed in every case. Since exophthalmos is frequently an indication of a threat to vision, if not to life itself, it seems important that this additional cause of proptosis receive attention.

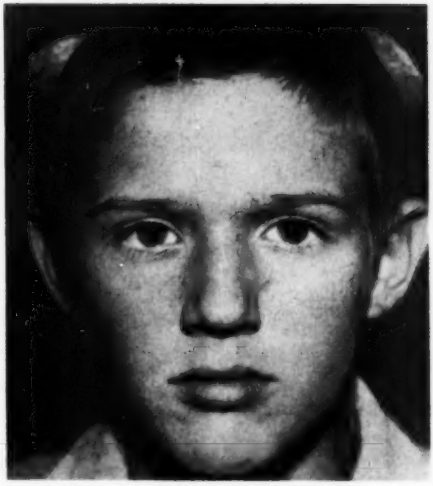

Fig. 1 (Case 1).—Boy of 12 years showing right exophathalmos and slight bulge of right side of head.

Report of Cases

CASE 1.—*A boy with headache, papilledema and right exophthalmos; diagnosis made on finding of enlargement of right middle cranial fossa; shift of ventricle to the left revealed by pneumoencephalogram; evacuation of hematoma through burr hole; prompt and lasting recovery.*

A white boy of 12 years (Fig. 1), previously in good health, without history of birth injury and without significant family history, complained of headache which began while camping as a Boy Scout. There was no history of injury. The headache was severe and constant, although it varied in degree; it was not localized and was accompanied by nausea at times. The visual acuity and fields were normal, and there was no diplopia. The right eye was prominent; 2 to 3 mm. of exophthalmos was measured, and a slight bulge in the right temporal area was evident, with asymmetry of the vault of the skull. The fundi showed 2 D. of papilledema with few striate hemorrhages.

Roentgenograms of skull revealed the calvaria to be asymmetric and the right middle fossa to be greater in all dimensions than the left and to encroach upon the adjacent orbit and temporal fossa (Fig. 2). The lateral wall of the orbit was indented by the expanded fossa, rendering this cavity shallow and, in effect, reducing its capacity. The superior orbital fissure was larger and the sphenoid ridge was sharp and elevated above the level of the left (Fig. 3). The temporal lines were fairly comparable. The optic canals were normal, and the sinuses were a bit asymmetric. The right temple bulged prominently. The diagnosis of subdural hematoma of the right middle cranial

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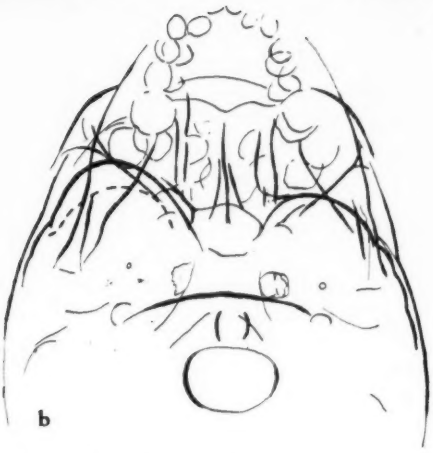


Fig. 2 (Case 1).—(*a*) Roentgenogram of base of skull showing greatly enlarged right middle cranial fossa with encroachment upon the lateral wall of the right orbit, reducing the capacity of the orbit and accounting for the exophthalmos. (*b*) Linear drawing of roentgenogram to clarify the esential features of the film.

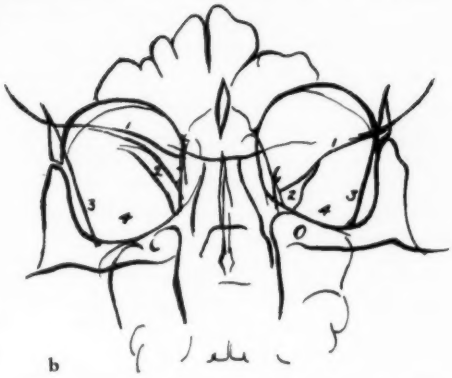


Fig. 3 (Case 1).—(*a*) Roentgenogram of orbits showing the marked asymmetry. Note the sharp and elevated sphenoid ridge and larger right superior orbital fissure as compared with the left and normal orbit. (b) Linear drawing of roentgenogram to clarify the essential features of the film.

fossa was made, and the patient was directed to the Neurological Institute.

Ventriculograms revealed moderate displacement of the ventricular system to the left, slight elevation of the right ventricle, and the temporal horn definitely higher than the left, suggesting a lesion underneath the temporal lobe. An arteriogram showed elevation of the right middle cerebral artery and its branches and dislocation of the circle of Willis on this side, indicating massive lesion in the right middle cranial fossa. Electroencephalographic studies were not helpful.

At operation a trephining was made in the right inferior parietal area with normal findings. Then another opening was made in the inferior temporal area, and a typical chronic subdural hematoma was found and evacuated of 60 to 80 cc. of liquefied blood having the color and consistency of "heavy machine oil." The usual sac of a hematoma was identified with the inner wall appearing unusually thick. After removal of the fluid,

which was under pressure at the beginning, the sac was irrigated freely and the brain was observed to return to its normal position with obliteration of the cavity despite the apparent thickness of the inner wall. A craniotomy was entertained for a later date to remove the sac, but the patient's course was so favorable and the recovery was so complete that this has not been necessary.

At this time, six years later, the patient is completing a preparatory course and will enter a leading university. His physical activity was restricted in the beginning because the margin of safety was unknown. It appeared as though the acute symptoms were the result of a second hemorrhage in an old sac as in Davidoff and Dyke's cases. But the absence of relatively fresh blood in the sac opposed this view, and the history of recent injury was also lacking. Follow-up films of the skull taken six years after operation failed to show any demonstrable difference in the right temporal fossa and the right orbit. The exophthalmos remained unchanged.

CASE 2.—*A girl with left exophthalmos and abducens paralysis due apparently to birth injury; demonstrable enlargement of left middle cranial fossa; removal of cyst (hygroma) resulting from hematoma; recovery.*

Fig. 4 (Case 2).—Girl aged 8 showing left exophthalmos and left abducens paralysis.

A white girl of 8 years (Fig. 4), with the complaint of left convergent strabismus since birth, was presented for study. Delivery was by forceps, with apparent injury to the left temporal region as evidenced by persistent bulging and prominence of the left eye. Attacks of unconsciousness and nausea and vomiting occurred during first years of life. Examination disclosed paralysis of the left lateral rectus muscle and 5 mm. of left exophthalmos. The eye was solidly proptosed and was without pulsation or bruit. The vision of each eye was normal and the left 20/40. The fundus of each was also normal. Confrontation fields were normal.

Roentgenograms revealed the calvaria to be symmetric and normal. The sella turcica measured 8×8 mm. The left middle fossa was greater in all dimensions than the right and extended forward to encroach on the adjacent orbit (Fig. 5). A well-defined crescentic deposit of calcium was present in the fossa. The lateral wall of the orbit was curved and displaced forward, causing this cavity to be shallow. The left superior orbital fissure was larger, and the sphenoid ridge was a bit higher in position. The lesser wing appeared thinned. The temporal line was well defined, but it was displaced slightly lateralward. The optic canals were similar in size and shape. All of the paranasal sinuses were fairly comparable.

The enlarged left temporal fossa, together with the crescentic deposit of calcium, indicated the presence of a subdural hematoma of long duration.

After encephalography an impression was recorded as follows: "A large subdural cyst communicates freely with the subarachnoid space. It has elevated the left temporal lobe, compressed and probably caused atrophy of the left side of the midbrain, and also the left side of the cerebellum. I think it might be large enough to produce some migration of the midline to the right" (Dr. Childe).

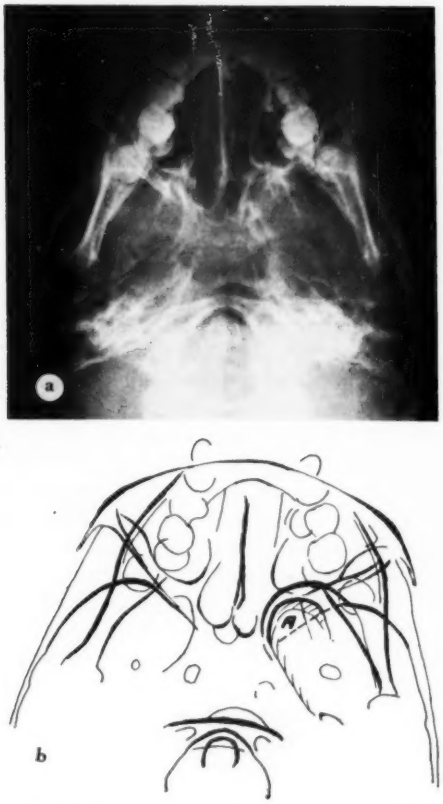


Fig. 5 (Case 2).—(*a*) Roentgenogram of base of skull showing greatly enlarged left middle cranial fossa encroaching upon adjacent orbit. Note the sickle-shaped deposit of calcium. (*b*) Explanatory linear drawing of roentgenogram. The calcium deposit is indicated by the letter *A*.

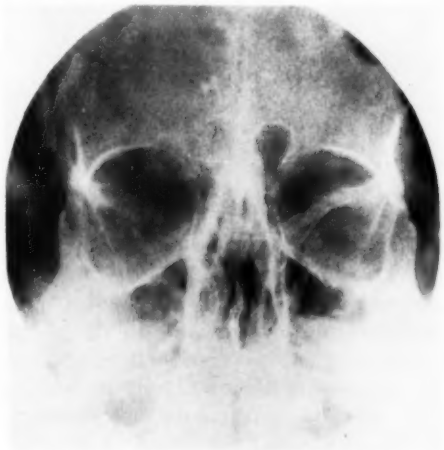
A left temporal craniotomy was performed by Dr. Wilder Penfield, and a cyst filled with yellowish fluid, occupying the entire fossa and elevating the temporal lobe of the brain, was found. The cyst was lined with a thick membrane which appeared to be much like dura. "A large portion of this was removed to permit the temporal lobe to pass down into the fossa without being trapped."

Dr. Penfield's final note was as follows: "This is a case of subdural cyst, which I suppose must be the end result of a subdural hematoma, that has become so well encapsulated that the covering resembled the dura itself. The fluid is clear and yellow. There was practically no remnant of an old clot. By continuous pressure within this cyst, the structures of the orbit must have been subjected to increased pressure from behind. I can see no reason why the protrusion of the eye should not subside completely. Hemorrhage of this sort might explain the history of paralysis, the history of sudden loss of consciousness and paralysis of cranial nerves in infancy."

This case is similar to the first in that a cyst or hygroma, which no doubt followed an early hemorrhage, was found. A dense shell of calcium was found by x-ray in the wall of the sac and suggested a longer duration. It seems probable that the failure to remove this shell accounts for the failure of the temporal lobe to reoccupy the temporal fossa after evacuation of the cyst.

CASE 3.—A boy of 14 was struck on the head by a baseball and developed symptoms of increased intracranial pressure 10 weeks later. Roentgenography revealed enlargement of left middle cranial fossa, and the arteriograms showed findings suggestive of a subtemporal subdural hematoma. At operation trephinings were made and the diagnosis was verified. Postoperative bleeding

Fig. 6 (Case 3).—Roentgenogram of orbits showing the asymmetry. The left sphenoid ridge is elevated; the lateral wall is greater in size in both dimensions, and the temporal line is less well defined. In the basal film the greatly increased capacity of the left middle cranial fossa was evident.



occurred, and a second operation was performed. Complete recovery followed the craniotomy, and there has been no recurrence after six years.

No history of previous injury could be elicited on careful search. Typical deformity of skull marked by enlarged middle cranial fossa and elevated sphenoid ridge was found 10 weeks after the verified injury. The left orbit was encroached upon by the enlarged fossa, and only 1 mm. of left exophthalmos could be measured. After six years the exophthalmos and the deformity of the skull seen by x-ray remain unchanged. The boy is well and is pursuing a college course.

CASE 4.—A white boy of 6 fell, striking his head, and soon after experienced headache, nausea and vomiting, and drowsiness. Six weeks later he had diplopia due to left abducens paralysis. Papilledema with hemorrhages developed. X-ray showed slight enlargement of the left middle cranial fossa, and the ventriculograms revealed a shift of the ventricular system to the right. Two millimeters of left exophthalmos was measured.

At operation a trephining was made in the left parietal area and more than 100 cc. of a brownish fluid was released through an incision in a bluish membrane. The diplopia and papilledema disappeared in a few days, and all symptoms were absent on discharge from hospital two weeks later. Three years later the exophthalmos was unchanged.

In this case a demonstrable enlargement of the left middle cranial fossa was evident in the x-ray films 2 months after injury.

Comment

Subdural hematoma may be found in patients of any age. It is not to be expected, however, that exophthalmos can appear as a sign of the lesion in any except those which might occur in the early and formative years when the skull is malleable and when the hematoma is subtemporal in position. It is to these cases that this discussion is confined. Injury of sufficient degree to rupture vessels would seem to be essential to all cases, but this is not borne out in the literature. All four cases of Davidoff and Dyke had second injuries, thus their title of "relapsing juvenile chronic subdural hematoma." Four of the nine cases of Bull which showed characteristic deformities of the skull in regular films gave history of injury. Recurrent injury was not mentioned in any of these. No history of injury could be obtained in our first case. Peet and Kahn [3] believed malnutrition could be a contributing cause of subdural hematoma. Doehle [4] considered that syphilis, rickets, diphtheria, and various chronic and debilitating diseases may play a role. Hugenin [5] attributed cases to hemorrhagic diseases, namely, pernicious anemia, scurvy, and purpura. Chronic alcoholism is not an uncommon cause of vascular pachymeningitis of Virchow,[6] which, according to Putnam,[7] is closely related to hematoma, but this can scarcely be considered in our young cases. In Kunkel and Dandy's [8] series of 48 cases of subdural hematoma of any location, a definite history of injury was obtained in 65%. Most of these occurred as a result of falls and automobile accidents. Acute lesions with fresh subdural clots were not included by Dandy, and all cases of fracture of the skull were also excluded.

Symptoms.—The symptoms of subdural hematoma are those of increased intracranial pressure, the commonest of which are headache, drowsiness, nausea and vomiting, and vertigo. Convulsions, visual loss, and diplopia are not uncommon. Localizing signs are seldom encountered. Papilledema was found in 53% of Dandy's series of 48 cases. Optic atrophy was rarely found. Thus, from these symptoms it can be seen that subdural hematoma can scarcely be differentiated clinically from intracranial tumor. If, however, these symptoms are associated with asymmetry of the skull and unilateral exophthalmos, hematoma should be considered.

Development of Symptoms.—Development may be concomitant with the injury or may be delayed for months or years. Putnam mentions Thibert, who described a probable case in which the symptoms were delayed nine years after the trauma. According to Schuberg, similar cases with longer or shorter intervals have appeared in almost every comprehensive article on the subject. Kasemeyer established beyond a doubt the fact of the not infrequent occurrence of cases with late onset of symptoms. The medicolegal importance of this is apparent. Such cases are often regarded as traumatic neurosis or psychoses of other sorts. But, what serves to activate the symptoms after the quiescent period?

Kasemeyer [9,10] was inclined to the opinion that merely the organization of a traumatic hematoma may give rise to repeated hemorrhages from rupture of capillaries. Experimentally produced hematomas in animals tend to regress, and this is against the assumption of repeated hemorrhage. It seems probable that hemorrhages recur in some cases with or without additional trauma and give rise to acute symptoms and that symptoms suddenly develop in other cases after a quiescent period without further bleeding. The latter would seem the commoner.

In 1925 Putnam wrote that there is something very mysterious about the occurrence of these lesions and their delayed relations to trauma. He considered that the source of the immediate hemorrhage was from rupture of the sinus, the lacunae, and the tributaries of the veins of the pia. Gardner [11] wrote that the vascular rupture occurs in one or more of the cerebral veins as they cross the subdural space to enter the longitudinal sinus. Munro [12] wrote that fractures of the skull and laceration and contusion of the brain are much more frequently the causative agents of the bleeding than rupture of a single vein. But the reason for the delayed manifestation of symptoms provoked considerable interest. Pathologic evidence did not support the simple hypothesis that continued bleeding was responsible for continued growth of the sac to the point where the brain was so compressed as to cause increased intracranial pressure. Gardner showed that the sac which forms about such a collection of blood has the characteristics of a semipermeable membrane. He believed that the enlargement of the sac depended on the passage of tissue fluids into the hematoma as a result of differential osmotic tension existing between whole blood and cerebral spinal fluid. Zollinger and Gross [13] found that the disintegration of the blood takes place slowly over a period of months and that the osmotic interchange of fluid into the sac proceeds accordingly at a similar rate. According to these authors, this explains the latent interval also. Dandy attributed the progressive symptoms and eventual death to increased intracranial pressure, for relief of the pressure preserves life. He believed the answer to be in the reaction of the brain to the hematoma as a foreign body. Tremendous areas of cerebral edema surround tumors of the brain, and this varies in degree with different tumors. Patients with intracranial tumors may be physically well one minute and unconscious or dead the next from increased cerebral edema and not from hemorrhage in the tumor. Similar factors, Dandy contended, are responsible for the gradual progression of subdural hematoma and the eventual death of the patient, i. e., the reaction in the brain to a lesion that already occupies a volume so great that the margin of security at any time is slight.

Pathologic Structure of a Traumatic Hematoma.—The structure consists of a fibrous envelope enclosing the clot which is in some stage of degeneration. The contents may vary from a fresh reddish-brown gelatinous clot to colorless fluid. A coffee-colored fluid is usually mentioned. An organized clot is seldom found. The conditions of the clot appear to have little relation to the length of the interval between trauma or onset of symptoms and operation or necropsy. Cant [14] found a quantity of yellow fluid and a small clot

in a case operated upon 45 days after injury. Brownish fluid was found in our fourth case 2 months after injury.

The fibrous capsule is composed of a very thin inner layer next to the arachnoid and a relatively thick outer or dural layer. The membrane next to the arachnoid consists of a thin sheet of connective tissue covered with a single layer of mesothelial cells. This is usually avascular and free from the adjacent arachnoid. The dural layer, in contradistinction, has a definite structure. This layer consists of fibrous tissue with large oval nuclei, is 1 to 4 or 5 mm. in thickness, and is distinct from the dura. Putnam described, as a characteristic feature of it, large irregular elongated spaces in the membrane near the dura, usually filled with red cells, leukocytes, fibrin, or granular debris. The adjacent dura is little altered, and the arachnoid may be discolored, fibrotic, or unaffected. The brain may be greatly displaced and compressed by the mass.

Since the formation of the hematoma in the middle cranial fossa in the young and malleable skull produces an enlargement of the fossa, this change should be demonstrable in regular and stereoscopic roentgenograms. According to the law of adaptation, which calls for an adjustment of the organ to the function which it is intended to perform, the middle fossa grows in capacity to accommodate the additional substance, i. e., the hematoma. This growth of the fossa encroaches upon neighboring structures. Anteriorly, the orbit is affected, and displacement and indentations of the lateral wall are seen which reduce the capacity of this cavity. This in turn displaces the eyeball anteriorly, producing exophthalmos. The eyeball shows a forward proptosis and no limitation of the excursions, unless paralysis of the abducens is produced, as has been noted in our second case. A bulge of the temple may be produced by the lateral expansion of the fossa. This change in the lateral wall of the orbit produces readily observable alteration in the usual appearance of the orbit in the films when compared with the contralateral or normal orbit. The superior orbital fissure is larger; the sphenoid ridge is sharp and elevated; the roof is shorter, and the temporal line may be displaced lateralward and obscured. This latter is due to bulging of the temple by the lateral expansion of the middle fossa. In addition, the bone of the lateral wall is greater in all dimensions and is thinner. Dyke mentioned thickening of the skull and hypertrophy of frontal and ethmoidal sinuses, but these observations could not be made in our cases. Basal films are essential to the indisputable recognition of enlargement of the middle fossa, and stereoscopic orbital films in the Caldwell position are necessary for the study of the orbital changes.

In my experience no other intracranial lesion has been encountered that has produced a similar skull deformity. Dyke had not found it in any other condition. Conceivably, a slow-growing glioma of the temporal lobe in a child could produce this deformity, but such tumors are not found in this position in children. Asymmetry of the skull, resulting from premature closure of sutures of one side of the vault, may grossly affect the base of the skull and the orbits, but enlargement of the middle fossa does not occur in these cases. Ultimately, perhaps, other causes may be found. The time required for these profound changes to occur is open to conjecture. Bull mentions one case in which the interval between the time of injury and the operation was only three months. Hardman [15] described the case of a boy of 8 with a bulging middle fossa who had been injured 10 weeks previously. Ten weeks was the duration of our third case and only eight weeks of our fourth case. Schuller, in a communication with Hardman, thought six weeks was necessary. Calcification of a portion of the wall would indicate a duration of years.

Ventriculograms and encephalograms show findings suggestive of this lesion. The lateral ventricles are usually asymmetric in shape and are displaced to one side, with one larger than the other. The subarachnoid sulci may be visualized and are seen to be

displaced from the inner table. Deformity of the basal cisterns may be distinguished if enough fluid is withdrawn.

Surgical Treatment.—The surgical treatment of subdural hematomas is imperative if life is to be saved, according to Munro. Without surgical intervention the mortality of 22 proven cases was 100%. With treatment, in his series of 39 cases, the mortality was 41.2%. Dandy, however, had a mortality of only 4% in his series of 48 cases.

Dandy and Putnam advocated exploratory puncture of the hematoma to establish its character and location. Then, with verification of the lesion, a small osteoplastic flap is recommended in order that the membranes of the lesion be removed, if possible. Reformation of the clot is not to be expected, according to Putnam, but cerebral edema is apt to occur in the lesion released from its long pressure. Dandy considered postoperative hemorrhage to be the chief complication. In two cases he evacuated the hematoma the second time, and in both fresh-clotted blood was removed. The bleeding arose from the raw edge of the outer membrane of the sac, which is usually very vascular. Constant and close postoperative care is a requisite if bleeding is to be detected and prompt measures instituted for its relief.

In many reported cases, as in our first and fourth cases, drainage of the fluid of the sac through a burr hole was all that was needed to effect permanent relief.

Summary

Another cause of exophthalmos is described as that which may result from deformity of the base of the skull induced by an infratemporal subdural hematoma in a young person. The localized increased pressure in the middle cranial fossa in a skull in the malleable state produces an enlargement of the fossa with encroachment on the adjacent orbit, making this cavity shallow and causing the eye to protrude. Demonstrable enlargement of the middle fossa in skull roentgenograms is virtually indicative of subtemporal subdural hematoma.

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Adenocarcinoma of the Meibomian Gland

A Pseudochalazion Entity

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Although Baldauf described some tumors of the Meibomian gland in 1870, it was Allaire in 1891 who first identified an adenocarcinoma of the Meibomian gland. Since that time there have been approximately 120 Meibomian gland carcinomas reported in the literature (Bibliography). The Meibomian gland carcinomas comprise about 0.2% of all lid tumors (Welch and Duke). It appears that generalized metastases have occurred in 12 of these cases. The incidence of metastases may be even greater than this, as a good many cases had inadequate or no follow-up.

In their early stages, Meibomian gland carcinomas are frequently mistaken for chronic chalazia. The distinction between these two lid lesions becomes particularly important because these tumors do possess metastatic tendencies. Recently, we have had several cases in which the clinical diagnosis was "recurrent chalazion," but the pathologic specimen proved to be an adenocarcinoma of the Meibomian gland. We now have collected a total of eight patients with Meibomian gland carcinomas for follow-up study from our files and from several colleagues. Six of these patients had an initial diagnosis of chalazion, and when the other two patients were first seen the diagnosis was readily apparent, as the tumors were far advanced.

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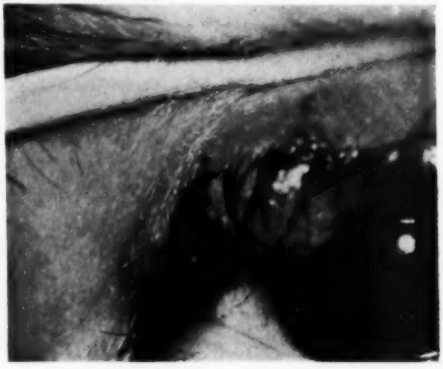
Report of Cases

CASE 1.—This 61-year-old white man was first seen in the Massachusetts Eye and Ear Infirmary (ME&EI) eye clinic on March 23, 1957, with a two-week history of a small nodule on the outer one-third of the right upper lid. It was felt that this was a marginal chalazion, and sulfacetamide ointment and hot compresses were prescribed. Three weeks later, the lesion was still present, and an incision and curettement was performed. When seen 10 days later, the lesion was healed.

Three months after the curettement, the patient noted that the lesion had recurred and was gradually increasing in size. Two more months elapsed before the patient returned to the eye clinic. At this time, a firm rounded tumor of the margin of the right upper lid was seen, which was traversed by blood vessels. The lesion was elevated above the surface of the lid (Fig. 1). A biopsy of the mass was done, and

Fig. 1 (Case 1).—Adenocarcinoma of Meibomian gland of right upper lid.



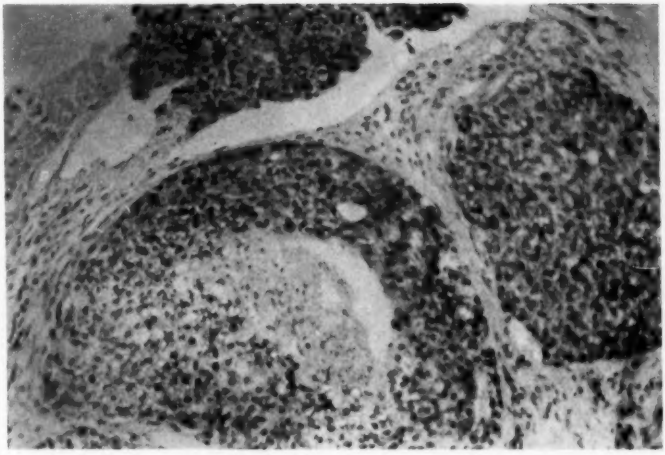


Fig. 2 (Case 1).—Formation of giant acini by large irregularly shaped polyhedral cells with vacuolated cytoplasm. Note numerous mitotic figures and central degenerative core. Reduced about 35% from × 100.

pathologic examination revealed adenocarcinoma of the Meibomian gland. Figure 2 shows the characteristic giant acini composed of large irregularly shaped polyhedral cells with vacuolated cytoplasm.

Two weeks after the biopsy, slight thickening occurred around the biopsy site but there was no gross evidence of recurrence. Two weeks later, a 2 mm. nodule was found under the skin of the right upper lid. This was felt to be a recurrence. At this time, the patient received 900 r in each of five treatments in the 100 kv x-ray machine without a filter through a 1 cm. circular field, with the eye protected. The patient received a total of 4,500 r over seven days. By the end of the radiation therapy, the nodule had disappeared and only a moderate skin reaction was present. There is no evidence of recurrence or metastasis eight months after radiation therapy was instituted.

Case 2.—This 72-year-old white woman was reported to have had a diagnosis in 1951 of a giant "chalazion" of the right upper lid of one year's duration. This was removed, and pathologic examination revealed a basal-cell carcinoma.

In 1953 another mass was found in the right upper lid which looked like a chalazion, and it was incised and curetted with complete recovery.

Four months later, another swelling developed in the right upper lid. It also resembled a chalazion, but it had multiple openings and emptying was accomplished by manual pressure.

One year later, the entire right upper lid was swollen with a granulomatous mass on the conjunctival surface. This was excised and sent to the same laboratory as had received the previous specimens, where a diagnosis of epidermoid carcinoma, Grade 2, was made.

Two months after this excision, the patient was first seen at the ME&EI eye clinic. Examination revealed a large red firm nontender mass replacing most of the right upper lid and covering most of the palpebral

Fig. 3 (Case 2).—Large firm nontender mass replacing most of the right upper lid.

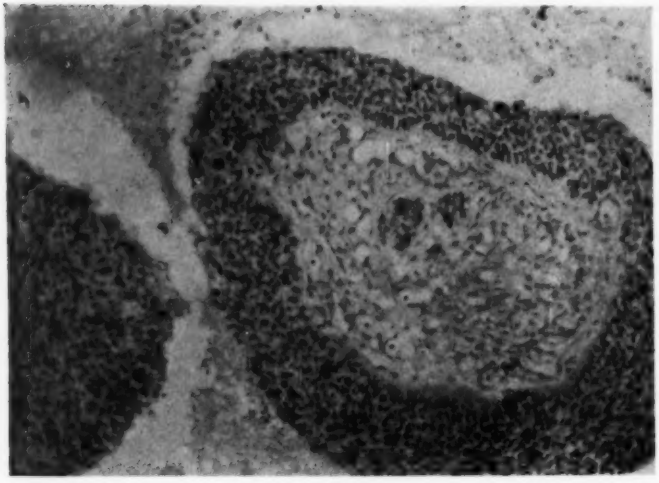


Fig. 4 (Case 2).—Giant acinus composed of vacuolated cells of various sizes and shapes with a central core of degenerated cells. Reduced about 30% from × 100.

fissure. There was some pale yellow secretion from an ulceration on the palpebral conjunctiva. No preauricular or cervical nodes were palpable (Fig. 3). A block excision of the mass was performed, and a plastic repair of the upper lid was done with a tarsorraphy. Pathologic examination revealed an adenocarcinoma of the Meibomian gland (Fig. 4).

Two months after the surgical excision of the tumor, the lid was completely healed with no evidence of recurrence. The tarsorraphy was repaired at this time. Shortly after this, the patient died of injuries sustained in an automobile accident. No autopsy was performed.

Case 3.—This patient was a 41-year-old Indian woman, who first noted a small swelling of the right upper lid in 1954. Her ophthalmologist believed this to be a chalazion, and it was excised six months later. It recurred within one month and grew bigger with ulceration on the palpebral conjunctiva.

Six months later she was seen by another ophthalmologist, in Surat, India. She presented a hard fixed swelling of the middle third of the right upper lid. The conjunctival surface was ulcerated, and there was evidence of old cicatrices. A complete excision of the tumor mass with total removal of the tarsal plate and about two-thirds of the upper lid was performed. Subsequently, a plastic repair was done with a good result. No evidence of metastases was found.

The specimen was sent to the pathology laboratory of the ME&EI, and a diagnosis of adenocarcinoma of the Meibomian gland was made.

The patient showed no recurrence or evidence of metastasis and had a good cosmetic result when last seen in the fall of 1957, that is, two years after surgical removal of the tumor.

Case 4.—This 74-year-old white woman was first seen in 1956, with a history of a "stye" on the lower lid of the left eye of one month's duration. Examination revealed a lid which appeared to have multiple chalazia with an elevated lid margin resembling a small papilloma. Multiple white cyst-like bodies were present beneath the conjunctiva vertically down the inferior fornix. An incision and curettement was done. Postoperatively, the small papilloma was still present on the lid margin.

Six months later the patient was seen again. The papilloma had grown to a 5×5 mm. mass. On the conjunctival surface the white cystic masses extended to the fornix (Fig. 5). An excision of the tumor was done and it was found to be an adenocarcinoma of the Meibomian gland (Fig. 6).

Fig. 5 (Case 4).—A 5×5 mm. mass of the margin of the left lower lid with subconjunctival extension, into the lower fornix.

Therefore, a large block resection of the lid was done with a plastic repair. No tumor was found at the margins of the second resection. The patient was last seen by her own ophthalmologist one year after surgery and showed no evidence of recurrence or metastasis; she has a good cosmetic result.

CASE 5.*—This 50-year-old white man was seen in 1948 with a painless ulcerative tumor of the upper lid of slow development. There was no history of trauma or previous inflammation. It was believed to be a chalazion and excised. Pathologic diagnosis was a Meibomian gland carcinoma. Recent follow-up has revealed no evidence of recurrence or metastasis.

CASE 6.—In 1956, this 41-year-old white woman was seen by her ophthalmologist concerning a small mass in her right upper lid of several months' duration. Clinically, the lesion had the appearance of an atypical chalazion, and an incision and curettement was performed. Because of the unusual consistency of the material removed, a specimen was sent for pathologic examination. This revealed an adenocarcinoma of the Meibomian gland (Fig. 7).

The patient was again seen in 1958, and a recurrence of the mass was noted, which the patient stated had been present for four to five months. Local excision of the lesion was performed, and again carcinoma of the Meibomian gland was found on pathologic examination (Fig. 8). The area healed uneventfully, and there has been no evidence of recurrence four months after surgery.

CASE 7.†—This 64-year-old woman was seen in 1952 with a six-month history of a mass in the right lower lid. She had a three-year history of chronic conjunctivitis and Meibomianitis. The right eye had been enucleated in 1950 for glaucoma and pain. Examination revealed a nodular mass in the right lower lid, extending into the orbit.

* Case 5 is reported by permission of Dr. Merrill Reeh.

† Case 7 is reported by permission of Dr. James Allen.

Fig. 6 (Case 4).—Low-power view of tumor shown in Figure 5, revealing it to be an adenocarcinoma of the Meibomian gland. Reduced about 30% from ×25.

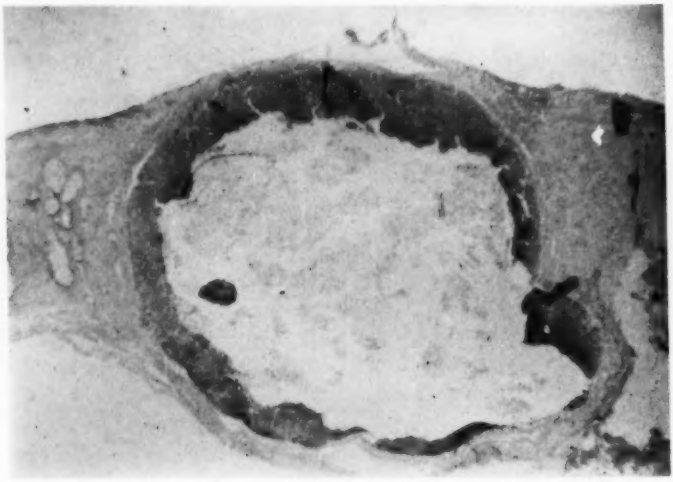


Fig. 7 (Case 6).—Cross section of right upper lid showing the development of a huge giant acinus composed of malignant cells, extending from skin to conjunctival surface. Note normal Meibomian glands on the left. Reduced about 30% from × 25.

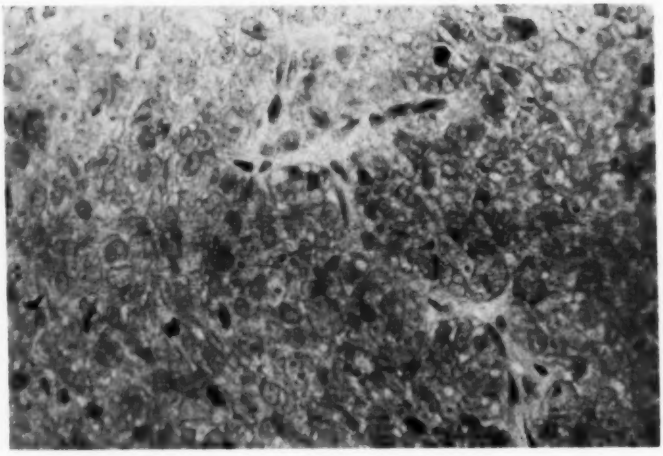


Fig. 8 (Case 6).—Details of the tumor cells. Polyhedral cells of varying sizes and shapes, with prominent nucleoli and vacuoles in the cytoplasm. Many mitotic figures are present. Reduced about 35% from × 400.

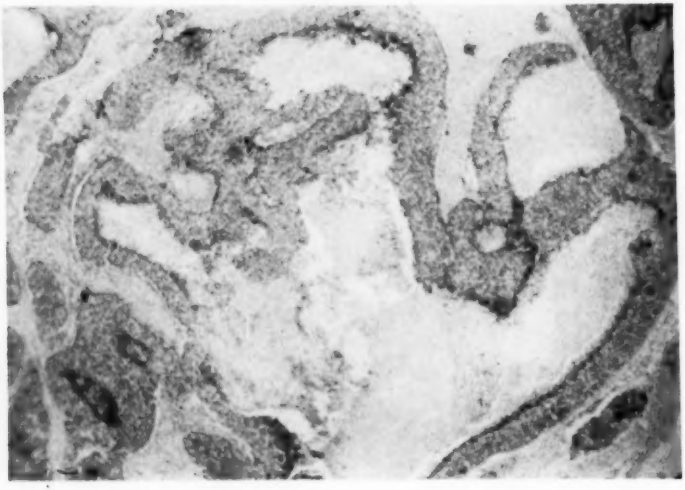


Fig. 9 (Case 7).—Dilated multiloculated giant acini with the central core filled with degenerated cells and secretion. Reduced about 30% from × 25.

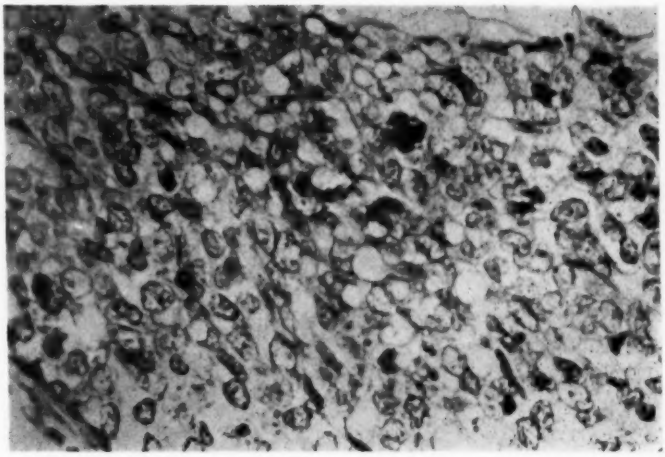


Fig. 10 (Case 7).—Cells are composed of nuclei of varying sizes with prominent nucleoli. The cytoplasm is filled with vacuoles. Numerous mitoses are present. Reduced about 35% from × 400.

No regional nodes were palpable. An exenteration of the right orbit was done. Pathologic diagnosis was adenocarcinoma of the Meibomian gland (Figs. 9 and 10).

Six months later, the patient was readmitted to the hospital because of the development of a small mass of suspicious-looking tissue at the apex of the exenterated orbit and a painless enlargement of the right preauricular node. At this time, all tissue was removed from the right orbit. Biopsy revealed a recurrence of the carcinoma of the Meibomian gland. Three weeks later, the right preauricular lymph node and surrounding parotid tissue were removed and a radical dissection of the lymph nodes of the neck was done. Pathologic examination of the tissue showed adenocarcinoma involving the lymph nodes in the tissue adjacent to the parotid gland. However, there was no involvement of the lymph nodes removed from the neck. Thirty-six hours after the radical neck dissection, the patient died of "cardiac failure." An autopsy was not performed.

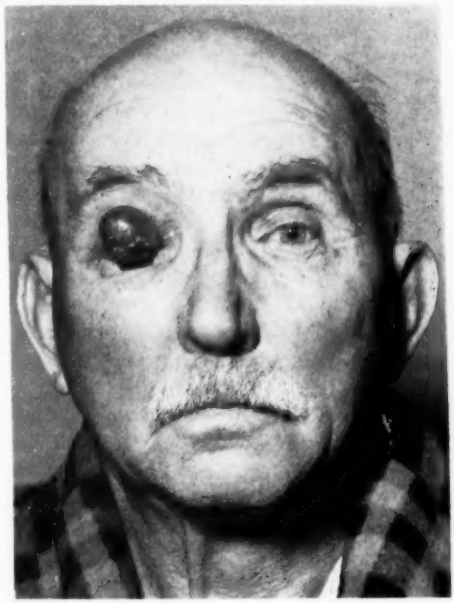
CASE 8.‡—In 1946, this 79-year-old white man noticed a small mass on his right upper lid. This was removed, but it quickly recurred four months later and gradually increased in size.

‡ Case 8 is reported by permission of Drs. James R. Duke and Jonas Friedenwald.

In 1952, a biopsy was done which indicated senile keratosis. The mass rapidly increased in size following the biopsy, and two months later he was admitted for treatment to the Wilmer Institute.

Examination revealed that the right upper lid was completely involved in a reddish-blue mass which was crusted on the anterior

Fig. 11 (Case 8).—A 2.5×2.5×2.5 cm. reddish-blue mass replacing almost entirely the right upper lid. The right preauricular node was palpable (by permission of J. R. Duke).



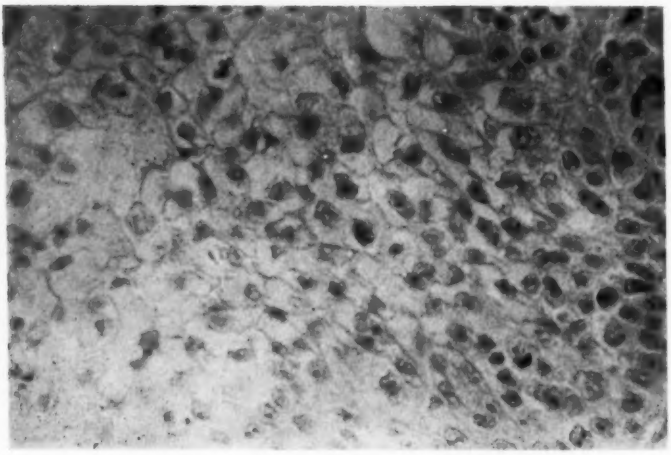


Fig. 12 (Case 8).—Cells are irregular in size and shape. Nucleoli are prominent, and the cytoplasm is vacuolated. Only a few mitotic figures are present. Reduced about 35% from × 400.

surface. The mass measured 2.5×2.5×2.5 cm. and was almost round. There was a yellowish purulent material coming from the inner canthus. The lower lid was red but not swollen. The eye was not involved. There was a small 1 cm. elongated preauricular lymph node on the right (Fig. 11). A biopsy of the mass was performed, which revealed adenocarcinoma of the Meibomian gland (Fig. 12). Therefore, removal of the right upper lid and the tumor mass was done, with a plastic repair by a sliding skin flap from the forehead. Also, the preauricular lymph node was removed and was found to be infiltrated with metastatic tumor tissue. The patient was transferred to the surgery service postoperatively for the question of radical neck dissection. However, this was not done because of the patient's reluctance.

Two and one-half months following the surgical removal of the tumor and preauricular node, the patient was readmitted to the surgical service because of palpable cervical lymph nodes. However, he again refused radical neck dissection.

Two months later, a biopsy of the right parotid region showed undifferentiated carcinoma. Because the patient refused radical neck dissection, a skin flap was elevated in front of the ear and he was given 2200 r at a depth of 1 cm. He was followed closely by the x-ray department without evidence of recurrence. However, during the next three months, the patient lost 30 lb. in weight.

At this time, physical examination revealed no evidence of local recurrence. However, on examination of the abdomen, a large mass was palpable in the right upper quadrant extending down to the midabdomen; it appeared to be attached to the liver. It was felt that the patient either had metastatic carcinoma to the liver or a primary carcinoma of the colon. Chest x-ray was negative, and arrangements were made for further study. However, the patient unexpectedly died while at home. It is not known whether an autopsy was performed.

Résumé

The average age of these patients at the onset of the tumor was 58 years, with a range from 41 to 79 years of age. Five patients were women, and three were men. The upper lid was the site of the tumor in six patients; the lower lid, in two patients. Six of the eight patients presented with a lesion which was interpreted and treated as a chalazion. The average time the tumor was present before appropriate therapy was instituted was two years, with a range from five months to five years. Two of the eight patients had metastases to the regional lymph nodes proven by pathologic examination. One patient had

radiation therapy alone; six patients had surgery, and one patient had a combination of surgery and radiation. Of the eight patients, five are alive and apparently free from recurrence and metastases at this time. Three of these five patients have been followed from one to nine years. Of the two patients who had lymph node involvement, one died one and one-half days postoperatively of "cardiac failure"; no autopsy was performed. The other patient died after a weight loss of 30 lb., with a mass in the abdomen, which was thought to be a large liver. However, we have been unable to determine if an autopsy was done. The third patient died as a result of an automobile accident, and an autopsy was not performed.

Comment

It should be emphasized that it may be very difficult to distinguish these tumors from a chalazion. They present a firm nontender painless nodule in the tarsus of the lid, which may appear slightly yellow on the conjunctival surface. As the carcinoma becomes farther advanced, however, its distinction from a chalazion becomes more evident. The tumor becomes fused to the lid margin. Later, there is swelling of the lid margin with some nutrient vessels visible over the tumor. The conjunctival surface may become umbilicated and ulcerated.

It would be ideal to examine every chronic chalazion for malignancy, especially in adults over 40 years of age. However, this is impractical; but histologic examination is indicated in any lesion which clinically resembles a chalazion and which fails to respond to the customary therapy or which recurs after spontaneous rupture. It has been observed clinically that if the tumor is incompletely removed or curetted, the growth of the lesion changes from that of a slow-growing tumor to that of an active malignancy with rapid recurrences and metastases (Lebensohn, 1935). Also, it should be remembered that a primary tumor may remain insignificant, while the metastasis reaches considerable size. Therefore, any small "chalazion" associated with a mass in the preauricular, orbital, parotid, or cervical regions should not be regarded as benign until proven so (Hagedoorn, 1934).

Summary

Eight cases of Meibomian gland adenocarcinoma are presented. The initial similarity of these tumors to chalazia and their metastatic tendencies is emphasized.

243 Charles St. (14).

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Peripheral Iridectomy with Scleral Cautery for Glaucoma

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This paper presents the results obtained in 70 eyes with primary glaucoma, with use of a new fistulizing operation previously described by me.[1] A fistula is produced by causing the lips of a scleral incision, made as for peripheral iridectomy, to retract by application of a cautery superficially to the wound edges. A preliminary report, based on experience with 42 eyes, indicated that the procedure could be used whenever a fistulizing operation was deemed necessary. It was effective in eyes with either wide or narrow angles and seemed of particular value in neglected acute and advanced narrow-angle glaucoma because of its simplicity and safety.

The operation resembles a peripheral iridectomy as performed for narrow-angle glaucoma. Rather than the small conjunctival flap employed for peripheral iridectomy, a large flap of Tenon's capsule and conjunctiva is reflected to the limbus as for any filtering operation. An *ab externo* incision is made perpendicularly in the sclera parallel to and about 1 mm. behind the limbus. As the angle of the anterior chamber is entered, a Hildreth cautery is applied superficially to the wound edges to cause the sclera to be contracted and the wound to gape. The perpendicular wound edges separate readily rather than slide over each other and remain in contact as they might do if they were beveled. The iris, particularly if the angle is narrow or the tension high, usually prolapses during application of the cautery, necessitating peripheral iridectomy. If the wound has not gaped sufficiently, further cautery can be applied after iridectomy. In some eyes the iris may prolapse immediately upon completion of the scleral incision. Iridectomy should then be done before application of the cautery. When this is done cauterization is more difficult because the flow of aqueous through the incision tends to cool the cautery. Greater heat, as provided by the copper-ball or Ziegler cautery, may then be advantageous. At times, especially in wide angle glaucoma, the iris may not prolapse, and a forceps is inserted into the anterior chamber to withdraw the iris for iridectomy. Following iridectomy and freeing of the iris pillars, the conjunctival flap and Tenon's capsule is sutured with running absorbable surgical sutures (gut), taking care to close both layers. Atropine is instilled, and only the eye operated on is patched.

The preliminary report summarized the results obtained in 42 eyes with primary glaucoma. Fourteen eyes had advanced narrow-angle, and twenty-seven eyes had chronic simple glaucoma. The tension was controlled, with normal tension in 26 eyes and with hypotony in 9 eyes. A round pupil was preserved, and the eyes had a remarkably unmutilated appearance. The cicatrices tended to be more diffuse and less polycystic than those following corneoscleral trephination. Many resembled the thick succulent scars of iridencleisis. Complications were few. An occasional hyphemia occurred, and, as with any filtering operations, occasional delay in reformation of the anterior chamber was encountered. The incidence of late complications could not be determined

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TABLE 1.—*Summary of Results Obtained from Performing Peripheral Iridectomy with Cautery on Seventy Eyes with Primary Glaucoma*

Type of Glaucoma	No.	Results			Reformation of Ant. Chamber				Complications, Hyphemia
		Controlled (Normotensive)	Controlled with Hyptony	Uncontrolled	3 Days or Less	1 Wk.	10 Days	2 Wk.	
Narrow angle									
Acute	13	12	1	0	10	2	0	1 (Saline injection)	0
Chronic	15	11	3	1	12	1	1	1	0
Congestive (2)									
Noncongestive (9)									
Total narrow angle	28	23	4	1	22	3	1	2	0
Chronic simple									
Angle narrow	16	6	5	5	8	8	0	0	3
Angle open	26	9	6	1	15	7	4	0	3
Total chronic simple	42	25	11	6	23	15	4	0	6
Sum total	70	48	15	7	45	18	5	2	6

TABLE 2.—*Results of Performing*

No.	Age	Sex	Race	Eye	Glaucoma		
					Type	Optic Nerve	Fields
1	48	F	W	O. D.	Narrow angle (chronic noncongestive)	Normal	Normal
				O. S.	Narrow angle (chronic noncongestive)	Normal	Normal
2	47	F	W	O. D.	Narrow angle (acute)	Normal	Normal
				O. S.	Narrow angle (acute)	Normal	Normal
3	43	F	W	O. D.	Narrow angle (chronic noncongestive)	Normal	Normal
4	46	F	W	O. S.	Narrow angle (acute)	Early optic atrophy.	Moderately constricted
5	70	M	W	O. S.	Chronic simple (angle open)	Moderate cupping	Superior arcuate defect
6	75	F	W	O. D.	Chronic simple (angle narrow)	Marked cupping	Nasal constriction
				O. S.	Chronic simple (angle narrow)	Marked cupping	Nasal constriction
7	74	F	W	O. S.	Narrow angle (chronic congestive)	Atrophy & cupping	Marked concentric
8	80	M	W	O. D.	Chronic simple (angle narrow)	Marked cupping	Marked nasal loss
				O. S.	Chronic simple (angle narrow)	Marked cupping	Marked nasal loss
9	59	M	W	O. D.	Chronic simple (angle narrow)	Normal	Normal
				O. S.	Chronic simple (angle narrow)	Marked cupping	Residual field
10	78	M	W	O. D.	Chronic simple (angle open)	Moderate cupping	Roenne step
				O. S.	Chronic simple (angle open)	Early cupping	Normal
11	65	M	W	O. S.	Chronic simple (angle narrow)	Normal	Normal
12	64	F	W	O. D.	Chronic simple (angle narrow)	Marked cupping	Marked nasal loss
				O. S.	Chronic simple (angle narrow)	Marked cupping	Roenne step
13	67	F	W	O. D.	Chronic simple (angle narrow)	Normal	Normal
				O. S.	Chronic simple (angle narrow)	Normal	Normal
14	70	M	W	O. S.	Chronic simple (angle open)	Marked cupping	Residual
15	56	F	N	O. S.	Chronic simple (angle open)	Marked cupping	Residual
16	60	M	W	O. D.	Narrow angle (chronic noncongestive)	Marked cupping	Residual
17	47	F	W	O. D.	Chronic simple (angle narrow)	Moderate cupping	Enlarged blind spot
				O. S.	Chronic simple (angle narrow)	Moderate cupping	Enlarged blind spot
18	51	M	W	O. D.	Narrow angle (chronic noncongestive)	Marked cupping	Residual
19	50	F	W	O. S.	Narrow angle (chronic congestive)	Marked cupping	Residual
20	75	F	W	O. S.	Chronic simple (angle narrow)	Early cupping	Baring of blind spot
21	65	M	W	O. D.	Chronic simple (angle open)	Normal	Normal
22	54	M	W	O. D.	Chronic simple (angle open)	Marked cupping	Marked loss
23	42	M	N	O. S.	Chronic simple (angle open)	Marked cupping	Residual temporal island
24	72	F	W	O. D.	Narrow angle (acute)	Normal	Normal
25	63	F	W	O. D.	Narrow angle (acute)	Pale	Markedly contracted
26	37	M	W	O. D.	Chronic simple (angle open)	Normal	Normal
				O. S.	Chronic simple (angle open)	Marked cupping	Marked loss

because the longest period of follow-up was one year.

The present report embodies an experience with 70 eyes operated on by this technique (Tables 1 and 2). All have been followed for at least two months, and some, for nearly two years. Twenty-eight eyes had narrow-angle glaucoma, and forty-three had chronic simple glaucoma. The tension was controlled, with normal tension in 48 eyes. Hypotony occurred in 15 eyes. It was not controlled adequately in seven eyes.

The anterior chamber was formed in 3 days in 45 eyes, 1 week in 18 eyes, 10 days in 5 eyes, and 2 weeks or longer in 2 eyes. These two eyes were in patients with advanced narrow-angle glaucoma, one with an acute attack of 10 days' duration. One developed an anterior chamber spontaneously, while the other recovered only after the injection of air. Hyphemia occurred in eight eyes, but in none did it interfere with the final outcome.

The operation seems particularly adapted to narrow-angle glaucoma where a filtration procedure is indicated. Thirteen eyes with acute glaucoma of more than 48 hours' duration were operated on by this method, and the tension was controlled in all but one. The attack had lasted for a week or more in several. Only one patient had a serious complication, which consisted of delayed

Peripheral Iridectomy with Cautery

Tension, Mm. Hg	Date of Operation	Results: Controlled (Normotensive)	Results: Controlled with Hypotony	Results: Uncontrolled	Postop. Tension (1955 Scale)	Reformation of Chamber, Days	Complications
Varied 35-62	7/24/56	x			17	1	None
Varied 35-62	7/17/56	x			21	1	None
62+	7/24/56	x			12	1	None
62+	7/25/56	x			17	1	None
26	8/ 4/56	x			21	1	None
62	11/ 2/56	x			17	3	None
40	11/13/56	x			24	3	None
46	4/18/57			(x)	(35)	(2)	(None)
	4/29/58 reop.	x			12	2	None
46	11/13/56		x		Less than 10	2	None
79	11/20/56		x		Less than 10	2	None
46	11/27/56	x			17	2	None
40	7/12/57	x			15	2	None
35	1/ 4/57	x			17	1	None
40	11/30/56			x	35	1	None
40	1/ 4/57	x			12	1	None
46	1/29/57	x			15	1	None
40	1/ 8/57			x	30	7	Hyphemia, absorbed 1 day
53	1/ 8/57		x		Less than 10	7	Hyphemia, absorbed 2 days
53	1/15/57		x		Less than 10	3	None
40	1/15/57			x	35	7	None
40	1/25/57	x			20	7	Hyphemia
46	1/17/57			x	40	2	None
46	2/ 7/57		x		10	1	None
53	3/12/57		x		Less than 10	14	None
40	3/19/57		x		10	7	None
40	3/12/57		x		10	2	None
40	3/22/57		x		Less than 10	4	None
83+	4/19/57	x			17	1	None
53	4/26/57			x	30	4	None
35	4/26/57	x			20	10	None
35	5/ 3/57		x		10	1	None
40	5/10/57	x			23	2	None
83	5/22/57	x			17	2	None
80	6/ 1/57	x			20	1	None
35	10/ 4/57	x			12	1	Massive hyphemia, absorbed 14 days

reformation of the anterior chamber, which persisted for over two weeks and necessitated air injection. Fifteen eyes were operated on for chronic narrow-angle glaucoma. The tension was controlled at a normal level in 11 eyes and hypotony in 3. Failure occurred in one.

The greatest number of failures, as well as hypotony, occurred in chronic simple glaucoma. Forty-three eyes were operated on. The tension was reduced to normal in 25. Hypotony resulted in 11. Hypotony was said to exist if the tension was 10 mm. Hg Schiøtz or under. The operation failed in eight eyes. There was little difference between eyes that had narrow or wide angles.

Comment

The results of performing peripheral iridectomy with cautery as a fistulizing operation in glaucoma have been analyzed in 70 eyes. The operation is easy to perform and leaves the eye with a relatively unmutilated appearance. The operation is safe and accompanied by few complications, the most serious being delayed reformation of the anterior chamber. Hyphemia occurred in eight patients of this series, but it caused no serious difficulty. In addition to being easy to perform, the operation has certain other advantages over more conventional fistulizing procedures. The danger of sympathetic ophthalmia should be minimal as compared with iridencleisis where the iris

TABLE 2.—*Results of Performing Peripheral*

					Glaucoma		
No.	Age	Sex	Race	Eye	Type	Optic Nerve	Fields
27	58	M	W	O. D.	Narrow angle (chronic)	Marked cupping	Residual
28	67	M	W	O. D.	Chronic simple (angle narrow)	Normal	Normal
				O. S.	Chronic simple (angle narrow)	Moderate cupping	Inferior arcuate
29	50	F	N	O. S.	Chronic simple (angle open)	Moderate cupping	Residual
30	57	F	W	O. D.	Narrow angle (chronic noncongestive)	Marked cupping	Marked loss
				O. S.	Narrow angle (chronic noncongestive)	Marked cupping	Marked loss
31	71	F	W	O. D.	Chronic simple (angle open)	Marked cupping	Marked loss
				O. S.	Chronic simple (angle open)	Marked cupping	Marked loss
32	62	M	W	O. D.	Narrow angle (acute)	Normal	Normal
33	50	F	W	O. D.	Chronic simple (angle open)	Early cupping	Normal
				O. S.	Chronic simple (angle open)	Normal	Normal
34	61	M	W	O. D.	Chronic simple (angle open)	Early	Full
35	41	F	W	O. D.	Narrow angle (chronic noncongestive)	Early	Arcuate
36	75	M	W	O. D.	Narrow angle (acute)	Can't be seen	Residual
37	60	M	N	O. D.	Chronic simple (angle open)	Marked cupping	Residual
38	67	F	W	O. S.	Chronic simple (angle open)	Marked cupping	Residual
39	72	F	W	O. S.	Narrow angle (acute)	No view	Normal
40	62	M	W	O. D.	Narrow angle (acute)	Normal	Normal
41	61	F	W	O. D.	Chronic simple (angle open)	No cupping	Normal
42	50	F	W	O. D.	Narrow angle (chronic noncongestive)	Marked cupping	Marked contraction
43	68	F	W	O. S.	Narrow angle (acute)	Normal	Normal
44		M	W	O. S.	Narrow angle (acute)	Normal	Normal
45	50	M	W	O. D.	Chronic simple (angle open)	Advanced cupping	Marked contraction
				O. S.	Chronic simple (angle open)	Early cupping	Marked contraction
46	54	F	W	O. D.	Narrow angle (chronic)	Central cupping	Normal
				O. S.	Narrow angle (chronic)	Cupping and pallor	Residual
47	52	F	W	O. S.	Narrow angle (chronic)	Normal	Slight constriction
48	44	F	W	O. D.	Chronic simple (angle open)	Normal	Slight constriction
				O. S.	Chronic simple (angle open)	No view	Normal
49	41	F	W	O. D.	Chronic simple (angle open)	Marked cupping	Normal
				O. S.	Chronic simple (angle open)	Moderate cupping	Normal
50	54	F	W	O. S.	Chronic simple (angle open)	Normal	Normal
51	39	F	W	O. D.	Narrow angle (acute)	Normal	Normal
				O. S.	Narrow angle (acute)	Normal	Normal

is incarcerated in the wound. Late infection should be less common than with corneoscleral trephination because the scar is thicker. Even when polycystic, it is usually thicker than that following trephination (Figure). The incidence of late cataract is unknown, but it will probably be comparable to corneoscleral trephination and iridencleisis. Fifteen patients had hypotony. This incidence seems comparable to that following corneoscleral triphination, but it is probably higher than that following iridencleisis.

The operation can be performed successfully as a secondary procedure in any meridian of the globe because it causes so little mutilation. When done nasally or temporally or adjacent to former sites of unsuccessful operations, such as iridencleisis, little further damage is done. The procedure is therefore of considerable value as an adjunct to other procedures.

The preferable position is at 6 or 12 o'clock, where the small coloboma of the peripheral iridectomy is covered by the upper or lower lid. When cataract formation is obvious and subsequent extraction imminent, the operation can be performed inferiorly, leaving the upper portion of the globe undisturbed for conventional cataract surgery. In eyes where this has been done, the tension has remained normal following extraction.

The operation seems particularly suitable for neglected acute attacks of glaucoma

Iridectomy with Cautery—Continued

Tension, Mm. Hg	Date of Operation	Results: Controlled (Normotensive)	Results: Controlled with Hypotony	Results: Uncontrolled	Postop. Tension (1955 Scale)	Reformation Chamber, Days	Complications
40	6/ 3/57	x			12	7	None
42	6/ 3/57	x			16	3	None
53	7/20/57			x	40	4	None
53	6/ 8/57	x			17	4	None
60+	7/ 9/57	x			22	1	None
32	7/20/57	x			20	1	None
30	7/30/57	x			15	1	Hyphemia, absorbed 9 days
30	8/ 9/57		x		Less than 10	3	None
27	9/24/57		x		Less than 10	2	None
80	9/13/57	x			15	1	None
46	9/17/57		x		Less than 10	6	None
40	9/24/57	x			20	6	None
35	10/ 4/57	x			24	1	None
46	9/24/57	x			12	1	None
53	10/25/57	x			24	3	None
35	10/29/57	x			17	3	None
46	10/29/57	x			20	9	None
60+	10/29/57	x			17	6	None
62	11/ 4/57	x			17	7	None
40	11/ 5/57		x		Less than 10	6	None
60	11/12/57	x			17	2	None
62+	11/14/57	x			17	2	None
62+	11/18/57	x				30 with saline injection	None
35	1/ 7/58	x			17	6	None
42	1/17/58	x			17	3	None
42	1/24/58			x		2	None
54	1/28/58	x			17	1	None
30	2/ 4/58	x			15	7	None
35	3/ 7/58	x			17	9	Hyphemia
40	2/14/58	x			21	9	None
36	3/18/58	x			12	1	Hyphemia, absorbed 4 days
36	2/18/58	x			12	6	None
62	3/18/58	x			15	6	None
59	3/19/58		x		Less than 10	3	None
22	3/21/58	x			15	3	None

Photographs showing filtering cicatrices resulting from peripheral iridectomy with cautery. *A* through *E*=12 o'clock meridian, *F*=6 o'clock meridian.

where iridencleisis is customarily advised. Such eyes are hyperemic and difficult to operate upon. The cautery diminishes the tendency to bleed, and peripheral iridectomy is easy to perform. In 12 such eyes no serious operative complication has been encountered and all have done nicely postoperatively. Failure to control tension occurred in one. Malignant glaucoma has not developed, but in eyes with very narrow angles it almost certainly will be encountered in the future. Although experience with the operation is still limited, I feel that it is definitely of value in primary glaucoma and that it can be used wherever a filtering operation is indicated. The relative value of

the procedure as compared to other operations must await the future.

Summary

My technique for peripheral iridectomy with cautery to produce a filtering cicatrix in glaucoma is described. Experience with 70 eyes indicates that this procedure can be used whenever a filtering operation is indicated.

313 S. 17th St. (3).

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The Normal Frontal Plane Horopter Discovered by Means of a New Device, the Horopter Finder

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Recently it occurred to me that, although seemingly harmful, the alpha angles might actually be helpful to sight because otherwise there would be no reason for their evolution. Their benefit might chiefly reside in effects on binocular vision and particularly upon the horopters. I tried to solve this problem of horopters and alpha angles by pondering over what is known of the optics of the human eye. This did not solve the problem at once but ultimately did so by bringing to light a fact that seems previously to have been completely overlooked. This fact is that, since within the binocular field the normal human eye sees all straight lines as straight,* it can, at least as concerns horopters, be treated mathematically as equivalent to a miniature camera with a lens perfectly corrected for spherical aberration, or with a pinhole instead of a lens. It is of paramount importance that in this camera the screen that receives the images is not curved like the retina, but is, as is usually the case with cameras, a plane perpendicular to the primary optic axis. In the eye spherical aberration is not corrected, as in the camera, by the optical system, but its effect on curvature of lines is certainly corrected in some way. This correction does not reside in the spherical shape of the eye, for this adds to the distortion to be corrected, but must depend upon the anatomical relationship of the retina to the occipital lobes of the brain. This anatomical correlation that, in spite of the curved retina and the marked spherical aberration, normally makes the eye equivalent to a perfect miniature camera is marvelous, but it must exist. Certainly there has been ample time for its evolution. The details of its evolution, and its embryological development, provide interesting subjects for speculation and investigation, but I need not discuss them here.

Suppose now that two such miniature cameras, identical in every way, are placed in a horizontal plane with their optical centers 6.2 cm. apart (my own interocular distance) and each pointing straight forward. Their screens would then be in the same plane. Assume that corresponding points are points whose distances and directions from the fovea are the same on both camera screens. If for the foveas the terminals of the primary optic axes were selected, the frontal plane horopter would be at infinity and all other midline horopters would conform to the circle of Mueller. If instead, there was selected for the fovea in the right camera a point to the right of this terminal, and in the left camera a point equally distant to the left of it, each camera would have an alpha angle, and of the same size. Assume that it is 5.5 degrees, the size I now know that my alpha angles actually are. There would now be an angle of convergence equal to the sum of the two alpha angles, that is, 11 degrees, and the bifixation point would be 32.19 cm. from the cameras. The horopter would now be a frontal plane passing through this bifixation point.†

It is to be noted that a circle of unchanging size of this horopter, no matter where,

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* I have sometimes observed that a straight line close to a curved line appears oppositely curved. This is a psychological phenomenon that has no bearing on the present problem.

† Those interested in the subject of aniseikonia will no doubt find helpful this conception of miniature cameras.

would be a circle on both camera screens, and always of the same size on the screens. No object on the horopter would have vertically disparate images. A straight line anywhere in the visual field would be a straight line on the screens. A curved line passing through the horopter could be a straight line on one screen but not on both. With the cameras on the same horizontal plane as assumed, vertical lines wherever situated would be vertical on both camera screens no matter where the bifurcation point and therefore always parallel or in line. This fact is important in connection with the question of cylindrical horopters. Mathematically, it is obvious that for the miniature cameras all midline horopters other than the frontal plane horopter are curved horizontally. Strictly speaking, the frontal plane horopter is the only surface horopter possible, since only on this plane is there no vertical disparity. However, many years ago I proved by stereoscopic tests, which I have since often repeated, that when an image is both vertically and laterally disparate with respect to its fellow it has the same stereoscopic effect as if it were only laterally disparate, provided the vertical disparity is not too great.‡ Moreover, in the case of contours vertical or nearly so, of which there are many in almost every view, vertical disparity is perceptible only at their ends. Hence, for both these reasons every point in the midline has a surface horopter passing through it, and this, except for the frontal plane horopter, is cylindrical. I realize that only in their horizontal midsections are these cylindrical surfaces truly horopteric, but I term them horopters because they serve perfectly as such for stereopsis.

It should now be obvious that, to two eyes that are equivalent to identical miniature perfect cameras, a frontal plane would appear flat when it was the frontal plane horopter, vertically cylindrical and convex when it was nearer, vertically cylindrical and concave when it was farther than this horopter.

Although, as I have explained, the normal human eye and the pinhole miniature camera are equivalent in certain important respects, they are far from so in two respects. The eye is markedly superior in that its spherical shape gives it a much wider visual field and markedly inferior in that its good visual acuity is limited to the fovea.

In my consideration of the miniature cameras, I have not allowed for the fact that normally in each eye the fovea is about 2 degrees below the optic axis. This error is so slight that it can be disregarded. Another error that I shall disregard as unimportant is the tacit assumption that the eyes rotate on their optic centers. That they do not accounts for the facts that the interocular distance and the midpoint between the optic centers change with movements of the eyes. I have also disregarded, and will continue to do so in this paper, the effects of torsional deviation and the distortion that may remain after correction of astigmatism by glasses. Torsional deviation that is not overcome by cycloduction would, of course, tilt the horopters according to its direction and amount.

Since in the tests to be described I have relied primarily upon my own eyes, I give the following details about my eyes. In each eye my visual acuity with glass is 20/15 or better. O. D., -0.25 s$=-1.00$ cyl, ax 115; O. S., -2.00 cyl, ax 60. The astigmatism causes considerable angular distortion, but this is almost completely overcome by my glasses. Up to the age of 30 years my eyes were slightly hypermetropic, and I had less than 0.50 D. of astigmatism in each. My ocular motor balance always has been well within normal limits. My acuity of stereopsis as determined by my stereopter is 20/10. My interocular distance with my visual axes parallel is 6.2 cm. Within the binocular field, with or without my glasses, I see all straight lines as straight. My visual fields are normal. My color perception is

‡ I also found that convergence could be induced by images with such disparity.

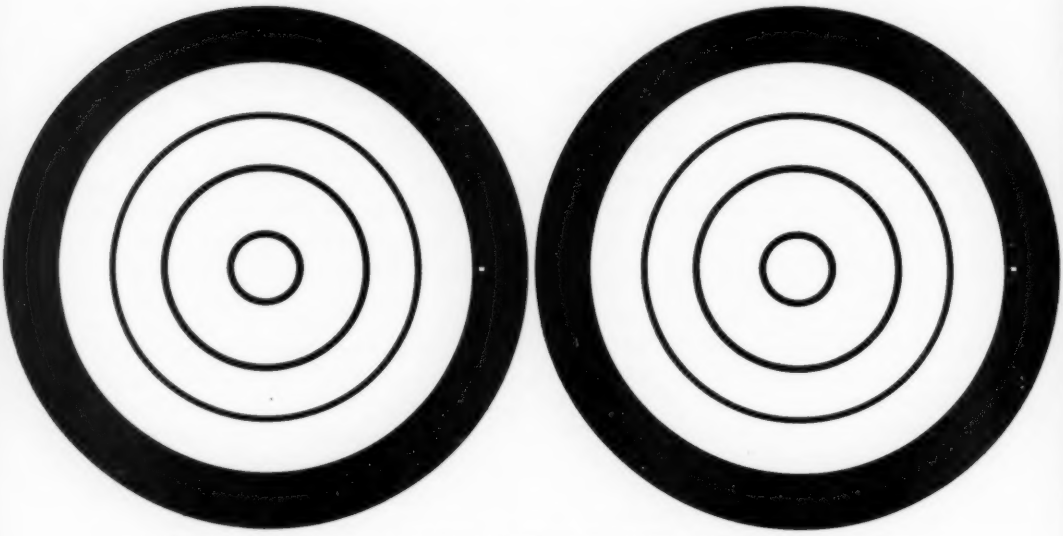

Fig. 1.—The two targets are as nearly identical as possible. When viewed in a Brewster stereoscope by normal eyes, the unified figure appears markedly concave.

normal. It is safe to assume that with my glasses before them my eyes are normal.

To confirm and amplify for real human eyes the facts derived from consideration of the miniature cameras, I have made the following tests and observations. In the first place I drew two identical figures on a card suitable for a Brewster stereoscope. Each figure consisted of five concentric circles, and the centers of the two figures were 6.2 cm. apart. (In Figure 1 the circles are fewer and the centers are 8 cm. apart to make the figures more suitable for viewing in a stereoscope.) The largest circles were each 6.2 cm.; the smallest, 7 mm. in diameter. When I unified these figures binocularly by relaxing my convergence, thus making my visual axes parallel, the unified figure showed an elliptical concavity about one-third as deep as it was wide. When viewed in a stereoscope the figure appeared about the same but larger.

So far as I know, this phenomenon has never previously been observed. For the observer it obviously proves that with his visual axes parallel or nearly so, his midline horopter is not a frontal plane, and that an actual suitably marked frontal plane of considerable size and at a considerable distance would appear to him concave. On the basis of this phenomenon, I contrived and constructed a device in which two planes, one before each eye, can be rotated equally but oppositely on their vertical axes. This reproduces, when viewed stereoscopically, the appearance of large single frontal planes seen binocularly at stated distances real or imaginary within a wide range. Because it locates the midline plane horopter, I shall call it a horopter finder.

The device consists of a cardboard base about 1 mm. thick, 18 cm. long, and 9 cm. high (Fig. 2). To this are firmly attached lengthwise two wooden supports for target planes. These supports are each 0.7 cm. thick, 2 cm. high, and 12 cm. long and are centrally placed. One is attached flush with the upper edge of the cardboard; the other, flush with the lower edge. The supports are therefore vertically 7.5 cm. apart. Two holes are drilled through each of the supports, for the pins that are to serve as axes of rotation for the target planes. These holes are each exactly 1.75 cm. above the base and 3.24 cm. laterally from the vertical

Fig. 2.—The horopter finder in stereoscope. The targets here shown are satisfactory, although somewhat less so than those in Figure 1.

midline. The upper two holes are therefore 6.5 cm. apart, as are the lower two.

The target planes, that is to say, the planes to carry the targets, each consists of a rectangular piece of cardboard 7.45 cm. high, 8.8 cm. wide, and 1 mm. thick. On the back of these are glued pieces of wood to receive the axis pins and give support to the target planes. The holes to receive the axis pins are 5 mm. below the surfaces of the target planes and 3.2 mm. from their median edges. At the median edge of each plane two small pieces of wood are glued, one on the inside and one on the outside (Fig. 2). These are so placed and so curved as to keep the tilts of the planes perfectly symmetrical by keeping the median edges always on the same level with respect to each other. The curves of the pieces of wood were perfected by trial and error (I leave to expert mathematicians the problem of describing them by equations). More such pieces of wood can be used to advantage. In some models I have used eight. A scale in degrees of arc is provided to indicate the tilt of each plane from their common level. A brake is provided so that the planes remain in any position they are placed. In the final model all visible parts except the targets are painted black. (To make its details more easily seen, the model shown in Figure 2 was not so painted.)

The model just described has a range of 27 degrees for each plane, much greater than needed for the purpose at hand. So far as I know, the method used for keeping two planes at the same but opposite tilts has never previously been employed for any purpose. I have also devised a different method for doing this that has enabled me to construct a model which has a range of 70 degrees for each plane and which not only permits the planes to be moved symmetrically, but when desired, each separately. This requires the use of two springs and a lever that impinges equally on the two planes. It is, therefore, more complicated than the other model. Nevertheless, it is simple enough, and even more accurate. I have spent many hours perfecting it, and to give all the small details of its construction would require too much space. Although made chiefly of wood, it has remained perfectly satisfactory for a long period. For permanency, it would be preferable to make it of aluminum. It could be advantageously made somewhat larger than my other model. Any need for this later model could be done away with by having two models, one like my original model and another like it except that the two planes would not be connected and must be moved separately. For the extra model, separate and especially accurate scales for the two planes would be necessary and also a brake for each plane so that it would remain wherever placed.

The targets that I first employed in the device, and have since found to be the best, were duplicate dials of thin cardboard with concentric circles, such as shown in Figure 1. They were attached to the planes by central pins and kept flat by peripheral pins. The heads of the central pins served as a central bifixation point. To compensate sufficiently for the prismatic elements in the lenses of the stereoscope, the distance between the centers of the targets when in the device was made 7.8 cm. This made it possible to use targets each 7.4 cm. in diameter. When the targets were used in

the device without the stereoscope, their centers were 6.2 cm. apart, my interocular distance. I may say here that under these conditions the effects were substantially the same with and without the stereoscope.

When viewed in the stereoscope with the targets on the same level, the appearance of the unified target is of course the same as in the phenomenon, that of a concave disc. By suitably tilting the planes the unified target can be made to appear flat or, to any reasonable degree, concave or convex. This is because the disparity produced is exactly the same as that produced by a large frontal plane at the point of convergence indicated by the scale on the horopter finder. When the scale indicates that the bifixation point is beyond infinity, the frontal plane is, of course, imaginary. Obviously when the unified target appears flat to the observer, it is conforming to his frontal plane horopter which is situated at a point of convergence indicated by the inclination of the two planes to each other. For me the target appears flat when the median edges of the planes are away from me and the two planes are at an angle of 11 degrees to each other—that is to say, when each plane is tilted 5.5 degrees. I confirmed this result by finding that with each plane tilted at an angle of 4 degrees the unified target always appeared concave and at an angle of 7 degrees, always convex, and in each case to about the same extent. Thus the horopter finder shows that I have a frontal plane horopter at a point of convergence of 11 degrees and therefore at a distance of 32.19 cm. from my eyes.

The apparent curvature produced by the horopter finder is possibly always elliptical, but the less the curvature, the more it resembles that of a sphere. By making the unified target appear highly curved, either concave or convex, it becomes markedly elliptical and the whole target takes on the appearance of the small end of a prolate ellipsoid with its horizontal meridian more sharply curved than its vertical meridian. It therefore appears elliptical in each of its three chief dimensions and closely resembles in shape the end of a hen's egg that has been horizontally compressed.

This remarkable ellipsoidal appearance would seem to refute the conclusion that all midline horopters other than the frontal plane horopter are cylindrical. Experiments that I shall describe, in which vertical lines instead of circles are used, prove that these horopters actually are cylindrical. Why the circles do not produce a cylindrical appearance is no doubt due to the fact that the upper and lower portions of the circles provide neither identical points nor lateral disparity, and therefore their depth is judged by the apparent depth of the lateral portions of the circles. This explanation is confirmed by the following simple experiment. A figure consisting of five concentric circles, the largest 7.5 cm. in diameter, is drawn upon a sheet of film and then bent in the form of a segment of a vertical cylinder. From a distance of 20 cm. it looks cylindrical, but from a distance of 52 cm. and farther it takes on the same appearance as the unified dial in the horopter finder, both when concave and when convex. Whatever the explanation may be, this experiment proves that an actual cylindrical segment when suitably marked with circles can give an ellipsoidal appearance.

So far as I know, the phenomenon which suggested to me the horopter finder is a new discovery, but many years ago two observers narrowly missed discovering it. In 1882 W. LeConte Stevens devised, and in 1897 Joseph LeConte discussed at length, a procedure in which tilting planes were used, but in a different way than in the horopter finder.[1,2] On each half of a stereoscopic card they drew an identical figure consisting of concentric circles, and then partly cut through the card in the middle so that the card could be "bent either way at any angle." When the figures were unified by convergence or in the stereoscope and the card was suitably bent, the elliptical appearances I have described were observed. The fact was not mentioned by either observer that the unified figure appeared concave when the unbent card was viewed in the stereo-

scope. In other words, the phenomenon I have described was not noted. LeConte's explanation of the appearances produced when the planes were tilted, was substantially, although not wholly, correct, but neither he nor Stevens indicated that he realized to the slightest extent that tilting planes could be used for the investigation of horopters and alpha angles, or for a test of any kind.

By two other methods I have corroborated the findings made with the horopter finder. In these tests, when a high degree of actual convergence was required I did not wear glasses, since the prismatic effects of decentering were too great. One method consisted in bifixating without glasses the center of a dial 24 cm. in diameter. The dial had five concentric circles and at first was at a distance of about 8 cm. Here it appeared strongly convex. On my moving back from it, the dial appeared to become flat at about 32 cm. This was in agreement with the horopter finder. It was impossible to be sure on my further movement backward that the dial became concave in appearance, doubtless because the visual angle it subtended became too small. I repeated this test using vertical lines as targets and at 8 cm. produced the appearance of a convex cylindrical surface. The difficulty of producing a concave appearance with a single target could no doubt be overcome by the use of a projection lantern and a large screen.

In the other corroborative method, I employed two identical contiguous dials each 20.5 cm. in diameter and placed on the same frontal plane. I unified these by convergence of my eyes and determined the bifixation point by means of a pencil point. When the bifixation point was at about 32 cm. from my eyes, the unified dial appeared flat; when the distance was reduced by my approaching the dials, the unified dial appeared convex. At a distance of 1.5 meters, it appeared distinctly concave.

Thus tests made as I have described on my own normal eyes with the horopter finder and in the other ways mentioned prove that I have a frontal plane horopter and that it is situated at a point of convergence of 11 degrees, that is, at a distance of 32.19 cm. from my eyes. Tests that I have made on numerous other persons with presumably normal eyes give substantially the same result. Hence this horopter is the normal frontal plane horopter. According to the concept of the miniature cameras, this means that if the two alpha angles are equal normally each is of about 5.5 degrees. This is in remarkably close agreement with Tscherning, who found by careful measurements with his ophthalmophanometer the normal alpha angle to be 5 to 7 degrees.

In the stereoscope the optical images are so distant, although they appear to be near, that differences in interpupillary distances have no important effect on the determination of the angle of convergence by the horopter finder. But, of course, the distance of the horopter for the same angle of convergence varies directly as the interpupillary distance. If C is the angle of convergence, I, the interpupillary distance, and D, the distance of the horopter, then

$$D=\frac{I}{2\ \tan.\ \frac{C}{2}}.$$

For a convergence of 11 degrees and an interpupillary distance of 6.2 cm., as in my case, the distance of the frontal plane horopter is 32.19 cm., as already stated, but for an interpupillary distance of 7.2 cm. it would be $\frac{7.2}{6.2}$ cm. greater, that is, 37.38 cm. Hence with a convergence of 11 degrees every difference of 1 cm. in the interocular distance would change the distance of the horopter by 5.19 cm. With my interpupillary distance, an increase of 2 degrees in the angle of convergence would reduce the distance of the horopter about 5 cm. and a decrease of 2 degrees would increase the distance about 7 cm.

In the horopter finder I have continued routinely to employ dials with circles, because I have found that the stereoscopic criteria that they present are much more readily accepted than those of any other targets I have tried. I have rather arbitrarily decided upon the number of circles and the width of the lines, but I have varied

these enough for me to feel sure that the dials finally decided upon are nearly if not the best possible for the purpose at hand (Fig. 1). Each is 6.35 cm. in diameter and has four circles including the largest, which has only one contour when on a black background. The smallest circle is 1 cm. in diameter, and the lines are each about 0.75 mm. in width. The number of circles is not highly important, but too many may cause confusion. A single large circle with a dot in its center, on each target, will produce effects similar to those produced by the multiple circles. It is, of course, of the utmost importance for each pair of dials to be as exact duplicates as possible. When they are imperfect in this respect, even when only slightly so, the circles cannot all be made to appear at the same level and may appear slanted with respect to each other, so that it is difficult for the observer to decide precisely when the unified target should be regarded as flat. Most of the targets I have made in ink with a drawing compass have been adequate, although none of them perfect. By photographing one well-drawn dial and having duplicate prints made, I have obtained perfect targets (Fig. 1), judging by the fact that with them all of the circles in the unified target can be made to appear to lie in the same plane. That this is so is alone conclusive proof that as concerns horopters the normal eye is equivalent to the pinhole miniature cameras.

It is especially difficult to draw duplicate targets composed of dots or straight lines, but I have succeeded in doing this with sufficient accuracy. With vertical lines I could produce with the device the appearance of a vertically cylindrical concavity of great depth and elliptical in shape. To flatten this I found that, as with the circular targets, it required an angle of convergence of 11 degrees. By increasing this angle, I could not make the unified target convex. Attempts to do this produced a feeling of discomfort. With large dots and letters of the alphabet, I was also unable to make the unified target appear convex. Why my mind refused to accept the stereoscopic criteria under these conditions I do not know. As I have already stated, under other conditions, perhaps more natural, I have produced the appearance of convexity when using vertical lines.

Even with the circular targets observers often require a few moments to perceive the stereoscopic effects and slightly longer to perceive the full depth. This is especially true when the small end of the ellipsoid points toward the observer—that is to say, when the figure appears convex. Whether or not the observer is employing adequate stereopsis can easily be ascertained by asking him to describe what he sees when the planes are moved, and by the precision with which he decides when the unified target appears flat. At first it is best not to make the unified target extremely curved but to place the planes each at about −5 degrees and, when the concavity is perceived, to place each plane at about +15 degrees, where marked convexity should be perceived.

I may now point out that with the photographically made circular targets, the horopter finder provides an excellent test for stereopsis. For without stereopsis no one could possibly see with the device the surprising appearances it produces. The test can be made quantitatively by determining, in degrees of equivalent convergence registered by the device, the shortest range at one end of which the target correctly appears concave and at the other end convex. A range of 6 degrees can be regarded as indicating an acuity of stereopsis of at least 20/20. When necessary, guessing can be reduced to a negligible factor by frequently repeating the test and changing the tilts of the planes at random while the observer's vision is obstructed. Hence with the horopter finder any person can determine his acuity of stereopsis and, if this is adequate, at the same time locate his frontal plane horopter and determine the sum of his alpha angles. However, for testing stereopsis the device would seem to be inferior to my stereopter, if only because it requires the use of a stereoscope.

The subject of the horopter is generally regarded as extremely complex, and an immense amount of literature bearing upon it has accumulated, but no definite conclusions can be drawn from it. Strangely enough, no one has previously suspected that the alpha angles are concerned in the matter. The horopter finder, by demonstrating that normally a midline plane horopter exists and that it is a frontal plane at about 32 cm. from the eyes, greatly simplifies and, to a major extent, solves the whole problem.

If it can be said that anything concerning horopters has been agreed upon, it is that the Herring-Hillebrand frontal plane horopter, situated about 2 meters from the eyes, is normal. This would mean an alpha angle of less than 1 degree for each eye. Among the many persons that I have tested with the horopter finder I have found, with one exception, none with an alpha angle that registered less than 4.5 or more than 6.5 degrees. As already stated, Tscherning objectively found the normal alpha angle to be between 5 and 7 degrees. A frontal plane at 32 cm., because it is within easy reach of the hands and at the usual distance for reading and fine work, is obviously more advantageous than one at 2 meters. To those with the really normal horopter, the apparent curvature of a frontal plane at 2 meters would be very slight, and this fact no doubt explains why Herring and Hillebrand did not detect it by their methods. In fact, the curvature of a frontal plane even at a great distance is too slight to be noticeable under ordinary conditions, for, as has been pointed out, to be easily recognizable, the curvature in question requires at a distance of about 5 meters a disc 1 meter in diameter with suitable configurations upon it, conditions seldom even approximated. This slight curvature of the visual field, instead of being harmful, might appreciably assist the monocular perspective in scenes or large pictures more distant than 4 meters, such as moving pictures.

It is now evident that the normal alpha angles, instead of being harmful as might have been supposed, are really advantageous, since they favorably locate the frontal plane horopter. They also provide other advantages not previously recognized. They produce astigmatism that, in regard to foveal vision, combats the astigmatism due to the elliptical shape of the cornea, and they make actual convergence of the eyes nil, or almost so, at the reading distance. No doubt it is because of their advantages that the alpha angles have evolved. It might be of some value to know whether there is a useful relationship between the kappa angle objectively measured on a perimeter and the alpha angle measured by the horopter finder. I have no important data bearing on this question.

It has been made clear that a person with normal eyes and a positive alpha angle of the same size in each eye has a frontal plane horopter at a midline bifixation point corresponding to a convergence of twice his alpha angle. All frontal planes farther away appear to him elliptically concave, and all those nearer, elliptically convex. If his alpha angles were nil, the frontal plane horopter would be at infinity and the midline horopter at any nearer fixation point would be cylindrical with the curvature of the circle of Mueller. At near distances, a frontal plane would appear perceptibly convex. If his alpha angles were negative, there would be no actual frontal plane horopter but there would be an imaginary one behind his eyes, and this could be located by the horopter finder. Thus a person with negative alpha angles, if he accepted his stereopsis, could never see a real frontal plane as flat, but with the horopter finder he could see his imaginary frontal plane horopter as flat. All real frontal planes would appear to him convex, the more so the nearer they were to him. Such persons must be exceedingly unusual, for I have not yet had one to test.

Questions next arise as to the effects produced by unequal alpha angles. I have not yet encountered this condition, but have simulated it by making the tilts of the two planes unequal in the horopter finder, yet making the unified target appear flat. This had the effect of tilting the unified target

on its vertical axis. Consideration of the miniature cameras agrees with this, showing that when the alpha angles are unequal there is no frontal plane horopter but there is instead a midline plane horopter that is tilted on its vertical axis. The angle of convergence for this horopter is, as before, equal to the sum of the alpha angles, and the angle of tilt of the horopter is half the difference between these angles. For these facts to be true, the distance of the fovea from the optic center must be the same in each camera, while the camera screens remain perpendicular to the optic axes. Therefore, when the alpha angles are unequal, one camera must have a longer focal length than the other. Otherwise, there would be aniseikonia.

With the horopter finder, when the alpha angles are unequal the distance of the horopter could be determined as usual, its tilt possibly perceived, and the amount of tilt estimated. However, the exact amount of the tilt could not be accurately measured by rotating the whole device in the stereoscope. Theoretically, without the device, the amount of tilt could be measured by centering perpendicularly on the bifixation point a large suitably marked plane and then rotating this plane on its vertical axis until it appeared to the observer to be perpendicular to the midline. The amount of this rotation would be the amount of tilt sought. When making this test it would be necessary to remove or neutralize any prismatic elements in the observer's glasses and to correct his aniseikonia by a lens. The accuracy of the result could be checked and possibly improved by tilting the two target planes separately in the horopter finder. If the subject had learned to allow for the tilt of his horopter, this method of measuring the difference in the alpha angles would not be reliable. However, if his allowance was so perfect that this test could not detect the tilt, the difference in his alpha angles would be of no importance to him.

I find with the horopter finder that a prism base-out increases and one base-in decreases the effect of the alpha angle of the eye before which it is placed. Therefore a prism base-out decreases and one base-in increases the distance of the frontal plane horopter. A 6$^{\Delta}$ prism before one eye or a 3$^{\Delta}$ prism before each eye changes the convergence angle for this horopter about 5 degrees. With a base-out prism, the distance of the horopter would be reduced for me about 10 cm. A 6$^{\Delta}$ prism base-out before each eye increases the effect of each alpha angle about 5 degrees and for me therefore reduces the distance of the horopter about 20 cm. I employed a 3$^{\Delta}$ prism to check my normal reading with the device, 5.5 degrees for each eye. With the unified target appearing flat at these angles, a 3$^{\Delta}$ prism base-out before one eye made it appear concave and this prism base-in made it appear equally convex. I obtained the same result with this prism when viewing an actual single dial 27 cm. in diameter at a distance of 32 cm.

The fact that prisms have these effects should be taken into account when they are prescribed for horizontal phorias. If the patient has a normal frontal plane horopter, prisms greater than 3$^{\Delta}$ for each eye should not be prescribed, for they would too greatly change the distance of the horopter. If the alpha angles were unequal they could, in effect, be equalized by prisms if the prisms were otherwise indicated. If a patient with negative alpha angles had esophoria, he could be benefited as to his horopter by correcting prisms. If he had exophoria, he would be harmed by the correcting prisms. Obviously, in some cases the horopter finder could decide between the use of prisms and operation and whether or not a deviation should be partly corrected by prisms.

With the factors alpha angles, angle of convergence, interocular distance, and distance and angular direction of the bifixation point from the interocular midpoint, it should be possible to derive an equation which would precisely define the curvature of any horopter. This has never yet been done, perhaps because it is not of any obvious practical importance. Meanwhile, assuming that the curvature of a midline horopter is the reverse of the apparent

curvature of the frontal plane passing through the bifixation point, any observer with adequate stereopsis can, by means of the horopter finder, estimate the curvature of any one of his midline horopters. However, since the exact character of a curve cannot be determined by its appearance, especially when it is seen in depth, the character of a horopter that is not a plane cannot be precisely determined by the horopter finder.

Summary

Consideration of a recently discovered stereoscopic phenomenon has led to the finding that it is dependent upon the alpha angles and that these angles can be measured by locating the midline plane horopter. On the basis of this phenomenon a horopter finder has been constructed that locates this horopter and therefore measures these angles.

The device reveals that each angle is normally about 5.5 degrees and that they produce a frontal plane horopter at about 32 cm. from the eyes, that is to say, within easy reach of the hands and at about the usual distance for reading and fine work. Thus the horopter finder proves that the normal frontal plane horopter is not that of Herring and Hillebrand, situated about two meters from the eye, but one situated at a much more advantageous distance. The alpha angles, therefore, are not harmful but actually helpful to sight. No doubt they have evolved because of this fact.

Observations made with this device, and in other ways, show that normally all midline horopters other than the midline plane horopter are cylindrical, concave when nearer and convex when farther than the frontal plane horopter. With the horopter finder, any person can, usually in a few moments, simultaneously determine his acuity of stereopsis, and, if this is adequate, the location of his frontal plane horopter and the sum of his alpha angles.

The facts, also shown by this device, that prisms base-out decrease and base-in increase the distance of the midline plane horopter should be given consideration when prisms are being prescribed for horizontal phorias.

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Annual Reviews

Cornea and Sclera

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I. Chemistry

In recent years ophthalmic physiologists and biochemists have been particularly interested in the factors concerned with corneal transparency. These factors include the physical structure of the cornea, its composition and chemical reactions, and the dynamics of water movement. A recent hypothesis advanced by Maurice concerning the corneal structure (presented in last year's review) postulates that transparency occurs because of a precise lattice-like arrangement of stromal fibers and cementing substances. The fibers are so related that all light is neutralized by mutual interference.[1] Any derangement of this precise structural make-up is followed by reduction or loss of transparency. Such derangement might occur with excess pressure, trauma, infection, or an increase in the water content above a critical level. To date no additional evidence has been presented to confirm this hypothesis.

In order to maintain transparency water must move in and out of the cornea at an unsaturated level. When the water content exceeds 75% to 80% of hyration, clouding begins. Several hypotheses have been presented regarding the mechanics of corneal deturgescence, and, of those under consideration, none explain all of the phenomena observed.[2] It is generally conceded that the epithelial and endothelial membranes constitute barriers through which water flows freely but passage of ions is limited. An earlier concept postulated that the corneal fluid content is maintained by the osmotic pressure of the aqueous and tears. This osmotic balance is dependent upon the integrity of the epithelium and endothelium, which act as semipermeable membranes. In vitro studies of corneal tissue have not borne out this concept.[3,4] More recently, evidence has been presented that movement of water and/or ions across the cornea is due to an active secretory process rather than simple diffusion. This secretory action requires energy output, and the transport mechanism is referred to as a water or sodium pump. The energy source for movement of water may possibly be in the epithelium. Acetylcholine is synthesized in the epithelium and is present in high concentration, indicating a high metabolic activity.[5] In clouded corneal grafts acetylcholine synthesis is significantly decreased.[6] Possibly the excessive hydration of the graft is related to impaired acetylcholine synthesis. However, to date neither the pump nor the substance transported (water or sodium) has been identified.

The water-binding quality of the collagen and mucoid of the stroma is another factor concerned in corneal hydration. The swelling pressure of the cornea is relatively great and occurs predominantly in the stroma.[7]

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Binding of water is assumed to take place in the collagen and ground substance, but the extent of this binding is not yet fully assessed. The fluid content of the stroma increases after disruption of the epithelium or endothelium.[8] It is greater after damage to endothelium, but the difference is probably due to the hydrostatic pressure of the aqueous.[9] On the contrary, passage of water through the cornea is greater after epithelial damage than endothelial.

Another major problem concerns the chemical composition of the cornea and the role of various chemical systems in metabolism. Corneal mucins compose approximately 14% of the dry weight of the cornea, and these mucins may occur either free or in combination with acid polysaccharides. Mucins are proteins or protein complexes. Mucoids are proteins bound with polysaccharides. Polysaccharides are polymers of basic sugars, such as hexoses and pentoses. When they yield an acid on hydrolysis they are termed acid polysaccharides. There are at least three free mucopolysaccharides in the cornea. These are chondroitin sulfuric acid A, chondroitin, and keratosulfate. Characteristically corneal collagen, as well as other collagen, contains three amino acids, glycine, proline, and hydroxyproline, and small amounts of sulfur-containing amino acids and tryptophane. Other important constituents include nucleic acids, lipids, phospholipid, cholesterol, ascorbic acid, glutathione, and riboflavin. The important ions are sodium, potassium, and chloride, and trace elements are iron, copper, manganese, and zinc.[10]

The corneal mucopolysaccharides differ from those in the sclera in that no keratosulfate is present in the sclera. These mucopolysaccharides may play an important role in the binding of water. Therefore, the quantitative and qualitative mucopolysaccharide content of the cornea should differ from that of the sclera. There is little doubt that a difference exists, but there is some conflict concerning the extent of these differences. Studies of embryonic and postnatal eyes with use of radioactive sulfate reveal that the collagen fibers develop early in the posterior corneal layers and fibrillogenesis spreads from the cornea to the posterior pole forming the sclera.[11] The anterior lamellae of the cornea are the last to form and are completed postnatally. Scleral metachromasia decreases with development, whereas corneal metachromasia increases. Resistance to hyaluronidase suggests that keratosulfate is formed late in development and appears in the cornea but not in the sclera. Also, sulfated mucopolysaccharides apparently appear earlier than the nonsulfated form.

Biochemical studies of the adult bovine cornea and sclera reveal the presence of chondroitin sulfate A, chondroitin, and keratosulfate in the cornea. Two fractions are found in the sclera which are assumed to consist of chondroitin sulfate B and a mixture of chondroitin sulfates A and C. No keratosulfate and only traces of hyaluronic acid are found. However, fractionation studies suggest that the difference in composition between the two tissues is more quantitative than qualitative.[12]

Radioactive-sulfate-uptake studies indicate that the mucopolysaccharides are in an active metabolic state.[13,14] Beef and rabbit corneas are capable of S^{35} uptake in vitro, and the uptake appears to occur in the acid mucopolysaccharides isolated from these corneas. The major fraction of the uptake appears to be related to keratosulfate. In vivo studies indicate that S^{35} uptake occurs in all major parts of the eye.[15] A considerably greater quantity of S^{35} uptake occurs in the sclera than in the cornea, and the turnover is much faster in the sclera. In the sclera the isotope is lost within 24 hours. By contrast S^{35} is demonstrable in the cornea for as long as 31 days. A major fraction of the S^{35} uptake appears in an esterosulfate which is probably bound to mucopolysaccharide.

Chemical determinations often serve as an excellent method of evaluating tissue metabolic activity in both health and disease. Phosphates are diminished in anaphylactic keratitis, which may signify a reduced metabolism in this disease.[16] However, nor-

mally phosphorous metabolism in the cornea is sluggish. The lipoid content in the cornea increases with senility and degenerations.[18] Many degenerations are specifically related to previous pathologic disturbances of the cornea, and abnormal concentrations of lipoid material usually signify previously existing disease. Glycolysis occurs predominantly, if not entirely, in the corneal epithelium, particularly in the basal layer. In corneal leukomas and corneal degenerations there is an appreciable reduction in glycogen concentration. This reduction is probably related to impaired metabolic function of the epithelium.[19] Glycogen is also found in inflammatory infiltrations in the stroma, the bulk of which appears in leukocytes. Carbohydrate metabolism of corneal epithelium is appreciably inhibited after hydrochloric acid burns.[20] Both glycolysis and oxygen uptake are reduced. Para-aminohippuric acid concentration in the aqueous is appreciably altered after hydrochloric acid burns of the cornea.[21] Alkaline burns of the cornea are generally conceded to be more serious than acid burns. This is due in part to the greater penetration of alkalis and their more widespread toxic effect. The primary opacity may be due to physical-chemical changes of the colloidal system of the cornea, in which mucopolysaccharides are released from their fibrillar structures into the interfibrillar spaces, with consequent interference with the optical system.[22] Hydroxyproline (an amino acid constituent of mucopolysaccharide) concentration increases rapidly after corneal exposures to acid or base. The return to normal is dependent upon the extent of the burn.[23]

II. Inflammations

A. Infections

1. *Virus.*—Viral diseases of the cornea command increasing attention each year. This interest appears to date from the widespread epidemics of keratoconjunctivitis that swept this country in 1941, and it is probably due to a variety of factors. For example, the impact of the epidemics of keratoconjunctivitis was severe and later became of world-wide concern. Consequently, the search for the causative agent was intense, and during this search a new virus strain important to ophthalmology was discovered (APC virus). Moreover, the incidence, complications, and visual impairments from viral infections on the American continent appear to have increased. Hence, the problem has become more important.

It is the purpose of this review to summarize some of the present concepts of viruses and virus diseases of the cornea.

Nature of Viruses: Viruses have been defined as "nuclear protein particles that are able to induce their own replication by susceptible host cells on which they are completely dependent and to which they are essentially foreign. This process of replication is accompanied by a detrimental effect on normal cellular function."[24] Microorganisms may be classified into four basic groups of which true viruses are the lowest in the scale. 1. Bacteria are the most complex and are capable of their own reproduction, have metabolic activity, and are not obligate parasites. 2. Rickettsia are less complex and are obligate parasites. These organisms have metabolic activity and are capable of reproducing, although requiring the aid of the host cell. 3. Viroid entities, such as trachoma virus, are even less complex but still possess some metabolic activity and are obligate parasites. They are entirely dependent on the host cell for replication. 4. True viruses, which are essentially nucleoprotein particles surrounded by a membrane, exhibit absolutely no metabolic activity.[25] For replication these organisms require both the building materials and the energy from the host cell.

In simplified terms, the life cycle of the true virus may be considered as follows: The virus protein molecule with its capsule is capable of eroding through the cell membrane and lodging in the nucleus. On entry it disappears for a period of time (eclipse phase), and on reappearance the protein molecule is stripped of its capsule. The cell nucleus then responds by creating similar

protein particles derived from its own structure. Ultimately the new particles are encapsulated and discharged from the cell. During this process of reproduction the necessary energy and materials are provided by the cell nucleus to the detriment of the cell. After discharge of the new particles, the life cycle is repeated and, since the participating cells are damaged or killed, pathologic tissue changes follow. Most viruses demonstrate a strong selectivity for tissues and have been classified as neurotropic, dermotropic, viscerotropic, etc. Since most corneal viral infections involve the epithelium, they may be considered primarily dermotropic. However, they may be capable of adapting to other cells.

If the observations of the characteristics and life cycle of the small viruses are largely correct, then several conclusions may be drawn. Medications, such as the sulfonamides and antibiotics, which act by interfering with metabolism or reproduction must be therapeutically ineffective. Clinical experiences to date appear to substantiate this. Hence, reports of successful medicinal therapy of such diseases as herpes simplex and keratoconjunctivitis must be considered suspect unless well substantiated. By contrast, large viruses which are metabolically active are susceptible to sulfonamides and antibiotics. To be effective for small viruses it appears that a therapeutic agent will have to act in the following manner: (1) prevent viral invasion of cells without destruction of the host, (2) eradicate infected cells without serious damage to the system, or (3) alter invaded cells in such a manner that they do not participate in viral reproduction.

Considering the life cycle of viruses, stromal involvement in some viral diseases of the corneal epithelium is puzzling. Such involvement cannot be due to a toxic effect of viruses, since small viruses are inert and secrete no metabolic products. Hence, it appears that stromal disease must be due to viral invasion and destruction of stromal cells. However, viruses have not been demonstrated within stromal cells. The presence of viruses within the tissue spaces (if this occurs) is not sufficient to explain stromal disease, since they are destructive only after cellular invasion. Yet, stromal involvement in herpes simplex keratitis, epidemic keratoconjunctivitis, and adenovirus infection obviously occurs. Possibly, stromal reactions occur from the toxic effect of secondary invaders or from breakdown products of epithelial degeneration or from metabolic disturbances of the complex chemical systems in the stroma created by epithelial damage. These inflammatory reactions in the stroma have not yet been satisfactorily explained.

An immune reaction probably occurs at the cell membrane, where an interaction takes place between antibody and virus in such a manner that erosion of the virus particle into the cell is prevented. Although the cornea is capable of immune response to viral invasion, unfortunately, it is of short duration in several important diseases. This is particularly true of trachoma and herpes simplex keratitis. This lack of immunity has made eradication of trachoma almost impossible in heavily infected areas despite effective therapeutic agents, since reinfection is high. Similarly, but for a different reason, recurrence of herpes simplex keratitis is also common. Apparently the herpes virus is constantly harbored by the tissues and when immunity is lost reinfection frequently occurs.[26]

Identification of a viral agent by laboratory means may be made by direct microscopic examination of smears and scrapings, by serologic tests, or by tissue-culture methods. Some viral infections induce a sufficiently characteristic cellular response to permit reasonable identification by microscopic examination alone. For example, characteristic inclusions in epithelial cells are often sufficient for diagnosis of such diseases as inclusion-body blennorrhea, molluscum contagiosum, and trachoma. Nevertheless, identification by microscopic examination alone has limited application. For many years identification of viral infections has depended largely upon serologic methods. These methods include the fol-

lowing ones: 1. Serum neutralization tests, in which a suspension of virus is mixed with equal volumes of diluted test serum and known negative serum. These serums are injected into susceptible animals which are then observed for a period of days. An absence of reaction indicates immune bodies in the test serum. 2. Immunity tests in which immune animals are given inoculations with variable dosages of the virus suspension. 3. Complement-fixation tests in which complement, a substance normally present in serum and a necessary constituent in the antibody-antigen reaction, is measured. When the content of complement is depleted after exposure of serum to suspensions of virus, evidence of immunity is established. 4. Precipitation tests, which rely upon introduction of antigen into immune serum, followed by the appearance of a precipitate when immunity exists. All of these tests have the disadvantage of requiring highly technical personnel and equipment. In addition, they require a long time period before a final diagnosis can be made.

For the past several years tissue-culture techniques have become very useful in viral identification. These methods became possible after discovery that sheets of epithelial cells could be grown in tissue culture. Dermotropic viruses are capable of invading these cultured epithelial cells, and in so doing they produce cytopathic changes that often characterize the disease. By this means a diagnosis may often be made within a matter of hours in contrast to the long delay by serologic techniques.

Herpes Simplex: More than 90% of the population over 15 years of age possess neutralizing antibodies to herpes virus, and the majority of the primary infections occur before 5 years of age.[27] The infection apparently persists for life in a latent form and is capable of recurrent overt manifestations. Infants are born with a passive immunity which is lost within six months. Of the primary herpetic involvements only a small fraction become overt. In children these overt manifestations are characterized by both local and systemic response, which most often appear in the form of a stomatitis. Onset is abrupt, and the symptomatology consists of fever, malaise, loss of appetite, and painful lesions about the mouth. In adults the primary infections are more difficult to recognize, but the clinical picture is one of systemic infection, with fever, malaise, loss of appetite, lymphadenopathy, and pharyngitis.

The ophthalmologist is most familiar with the recurrent lesions appearing in the cornea. Onset of keratitis may be precipitated by injury, either physical or chemical, including previous corticosteroid therapy.[28] The mechanism of this relationship has not yet been determined.

The classical dendritic figure is the commonest lesion found, and its appearance is diagnostic. Variations include the geographic-map ulcer, stellate lesions with multiple dendritic figures, and, in long-standing cases, filamentous keratitis.[29,30] Often there are associated lesions, such as follicular conjunctivitis, conjunctival ulcers, and herpetic ulcers of the lids and mucous membranes around the mouth. The corneal lesions are amazingly asymptomatic, which apparently relates to severe loss in corneal sensitivity.[31,32] This reduced sensitivity is often a diagnostic aid. The keratitis is often recalcitrant to all types of therapy and not infrequently is followed by disciform keratitis, uveitis, uveoscleritis, and even hypopyon ulcer.[33]

Several diagnostic laboratory aids are available and in the more chronic lesions are essential for establishment of the causative agent. In acute lesions intranuclear inclusions are often demonstrable. More recently multinucleated giant cells have been described in the scrapings of the epithelium.[34] These giant cells occur only in herpes simplex, varicella, and herpes zoster. Herpes simplex is easily distinguished clinically from the other two diseases. The giant cells vary in size from relatively small cells containing only a few nuclei to very large cells containing many. They are easily recognized under low magnification. A typical cell contains up to 15 nuclei. The cytoplasm

is scant and stains light blue with Giemsa stain.

Inoculation of rabbit eyes is also a useful technique, since the rabbit cornea is unusually susceptible to the disease. Serologic tests have limited application and apparently are useful only to distinguish primary herpetic infection.[35] Tissue-culture methods are excellent, since the virus readily invades the epithelial cells and produces typical cytopathic changes.[36]

Although there are continued reports of beneficial effects from various drugs, no proven specific therapy has yet been found. Chlortetracycline in combination with cortisone has been advocated.[37] However, the deleterious effects of cortisone and other steroids has been well established and should be avoided. γ-Globulin may be effective when injected subconjunctivally.[38] This may function by increasing the antibody content of the cornea, but, considering the avascularity of this structure, the effectiveness of this therapy seems dubious. Naphazoline, lysozyme, and alcohol solutions of undecylenic acid have been reported as effective.[39-41] Irradiation seems to enhance the immune response of epithelial tissue to infection.[42] Radiotherapy may be of value, but probably the benefit gained (if any) is outweighed by the potential danger of the treatment.[43] In the final analysis, removal or destruction of the corneal epithelium appears to be the most satisfactory.[44,45] It may be accomplished by simple denudation or by application of a thermophore. This therapy has some scientific basis, since it eliminates the host cell in the life cycle of the virus. The addition of iodine, ether, or alcohol probably is of little benefit.

Trachoma: The course of trachoma has been artificially divided into four stages. While useful in designating the phase of the disease, this classification tends to divert attention from the basic pathogenesis of the process. Tissue responses to viral invasion are not only degenerative but may also be proliferative,[46] nor is all detrimental change primarily due to the virus itself. This is probably the situation in trachoma. The trachoma virus is dermotropic and, hence, invades only the epithelial cells of the conjunctiva and cornea.[47] Initially the infection is superficial (Stage 1), which is clinically characterized by hyperemia and irritation. The tissues also respond by formation of characteristic follicles, which are said to be distinguishable from other follicular eruptions by their cellular content. These include numerous macrophages containing engulfed cellular debris (Leber cells) and plasma cells, which are rarely seen in nontrachomatous disease.[48] Inclusion bodies are also demonstrable. As the disease progresses, there is epithelial proliferation with growth into the underlying tissue.[49] The trachoma virus in the deeper epithelium is then less accessible. Since immunity is low, the virus continues to reproduce and reinvade cells, which accounts for the chronicity of the disease. Chronic inflammation of the substrate is a constant response to the continued epithelial damage. As in all inflammations, there is a continued attempt at repair, which stimulates excessive neovascularization and fibroplasia. Consequently, there is destruction of the secreting glands and cells of the ocular mucous membrane, with desiccation of the globe surface. Ultimately, the tarsal plate is distorted or destroyed and extensive neovascularization of the cornea occurs (Stage 4).[50,51] In effect, then, the destructive changes may be attributed to continuous inflammation, precipitated by epithelial damage, and not to actual viral invasion of the mesoderm. The reversibility of these tissue alterations is directly proportional to the extent of scarring. Late in the disease reversal is no longer possible. Finally, the disease burns out because the environment for replication of the virus cells probably is no longer favorable.

Diagnosis of the disease is usually very simple in heavily infected areas. It is derived from the clinical appearance of the follicles, conjunctival reaction, and pannus of the upper cornea. The clinical diagnosis can be verified by finding inclusions in the scrapings and from the type of cellular re-

action.[52,53] Classically, the inclusions are identified by Giemsa stain; however, staining with strong iodine (Lugol's) solution is more rapid, and it stains more inclusion bodies with better detail.[54] The disease can be confused with other conjunctivities, and occasionally it is necessary to resort to more complex serologic laboratory procedures.

In the past, studies of the virus have been hampered by the inability to reproduce the disease in small laboratory animals. It is primarily a disease of humans but can be reproduced in a mild, abortive form in baboon and monkey.[55] However, it now appears that small laboratory animals may be inoculated with the disease and the trachoma virus recovered.[56] Although these animals do not develop clinical symptoms, the viruses have been recovered from the anterior chamber and the testes of rabbits and intranasally from mice. Passage through the rabbit testes is probably the most satisfactory. Viruses have also been recovered after the inoculation of chick embryos.[57] These findings have not been verified.[58]

The treatment of indvidual cases of trachoma is now relatively simple. The disease responds well to prolonged instillation of sulfonamides and antibiotics, particularly chloramphenicol and the tetracycline group.[59-69] Medications may be applied in the form of drops, ointments, and subconjunctival injections or systemically. Regardless of the mode of application, a cure can be obtained within a matter of weeks if a reasonable schedule is maintained. Kynex (sulfamethoxy-pyridazine) is an effective new antibiotic which has the advantage of being long-acting and achieves prolonged high blood level from a single dose.[48] Local administration of 1% emulsion of Synthomycin may be effective if given by injection and continued for a period of two months after clinical improvement is noted.[70,71] Determination of a cure may be difficult, since subsidence of clinical symptoms does not necessarily mean that the organism has been exterminated. Apparently, an exacerbation of the disease can be precipitated by local administration of corticosteroids.[72,73] If the administration of corticosteroid is not followed by an exacerbation, the disease may be considered as cured.

While effective therapy of isolated cases is relatively simple, mass therapy of heavily infected areas presents a different problem. Temporary marked improvement following limited mass therapy in local areas has been reported.[74-76] However, despite the availability of effective drugs, the incidence of trachoma has not been appreciably reduced on a world-wide basis. This failure of mass control can be attributed largely to the lack of acquired immunity. Fractional cures of heavily infected populations are inadequate, since the reinfection rate is exceptionally high. Other important factors include lack of adequate amounts of antibiotics and sulfonamides, poor hygiene among heavily infected peoples, and a lack of cooperation on the part of the peoples involved. Apparently, adequate control will not be obtained until effective medications are coupled with effective methods of suppressing reinfection.

Epidemic Keratoconjunctivitis: After the epidemics of keratoconjunctivitis that first appeared on the North American continent in 1941, an intense search for the causative agent began. The characteristics, symptomatology, and objective findings indicated that a common agent, probably a virus, was involved. In 1954, a new viral strain was isolated from persons suffering with respiratory infections. The disease was characterized by adenitis, pharyngitis, and conjunctivitis. This strain of virus was first referred to as APC virus and now is most commonly called adenovirus. A total of 18 human and 5 simian serotypes have been established by an agar-diffusion technique.[77] Of these, at least 3 types (Types 3, 7, and 8) and possibly more are capable of producing a keratoconjunctivitis that strongly simulates the epidemic variety.[78-85] Type 8, in particular, has been isolated by tissue-culture methods or identified by serologic techniques in most, if not all, epi-

demics of keratoconjunctivitis of recent years.[86-89] Furthermore, serologic methods have incriminated adenovirus in most epidemics since 1951 but have not established that the original epidemics were necessarily due to this agent.[89,90] The evidence pointing to adenovirus was strengthened after inoculations in human volunteers by Type 8.[91] Typical keratoconjunctivitis occurred with clinical onset evident in 7 to 10 days after inoculation and lasted three to four weeks. The virus was recovered from the infected volunteers. Like epidemic keratoconjunctivitis, the present adenovirus epidemics have world-wide distribution.[92-95] However, despite the evidence that adenovirus is presently responsible for a large incidence of keratoconjunctivitis, caution has been advised against considering it the sole cause.[96]

The period of infectivity of an active case is approximately 15 days, and the disease is probably spread by direct contact with infected persons or materials.[97-99] To date, treatment has been symptomatic, although a neomycin hydrocortisone ointment has been reported as effective.[100]

To summarize the available data, it appears that adenovirus, particularly Type 8, is largely responsible for epidemics of keratoconjunctivitis of recent years. The symptomatology and clinical and laboratory findings simulate those of the epidemics of earlier years. This suggests that adenovirus was probably related to the original epidemics but not necessarily the sole cause.

2. *Bacteria.*—Bacteriologic findings of corneal disease probably vary with geography as well as with time. As late as 1940, pneumococci were most frequently found in central corneal ulcers.[101] In a recent bacteriologic survey of keratitis, Pseudomonas aeruginosa was the organism most frequently isolated. Other organisms included micrococci, streptococci, hemophilic bacilli, and nonpathogenic staphylococci. Mixed bacterial flora were not uncommon. Previous treatment, particularly with antibiotics, appreciably decreased the incidence of significant isolations. Another survey of 1,812 bacteriologic examinations of ocular adnexa, vitreous, aqueous, and blood in infectious eye diseases revealed that Staphylococcus pyogenes var. albus was most frequently found, followed by Staphylococcus pyogenes var. aureus, streptococci, and Gram-negative rods.[102] A comparison of the bacterial flora of traumatic ulcers in coal miners and nonminers revealed fewer pathogenic organisms in the traumatic ulcers of the miners.[103] Although iridocyclitis is the commonest ocular involvement in brucellosis, a severe keratitis may also occur.[104] Extensive corneal damage is one of the characteristics of Pseudomonas ocular infections. This destruction may be due to a proteolytic enzyme secreted by the organism, which requires an appropriate protein substrate in the cornea for enzymatic function. The proteolytic enzyme responsible for the corneal destruction is not necessarily inherent in all organisms.[105] Epidemic conjunctivitis due to Koch-Weeks bacillus may be effectively treated with local administration of penicillin, and prophylactic instillation of this drug will protect eyes exposed to the disease.[106] However, prophylactic administration of antibiotics is usually impractical because of the existence of many strains of bacteria resistant to most antibiotics.[108]

3. *Fungus.*—Fungus infection should be suspected in all classic corneal ulcers, particularly if prolonged steroid or antibiotic therapy has been previously administered. Local administration of steroids and wide-spectrum antibiotics apparently inhibit the growth of saprophytic organisms of the conjunctival sac and thereby disturb the balance between bacteria and fungi normally present.[108-111] Very few effective antibiotics are available for such infections. Nystatin is probably the best for general use, but topically applied iodine solution may also be effective.[112-114] Trichomycin may be of value for ulcers infected with Candida albicans,[115] and for shallow ulcers keratoplasty may be employed.[116]

B. Nonspecific

Hypersensitivity accounts for a significant incidence of corneal disease. Superficial corneal ulcers have been related to cosmetics, chocolate, and exposure to pollen. Marginal ulcers are probably related to bacterial allergy, and interstitial keratitis and corneal clouding following keratoplasty are probably due to tissue hypersensitivity.[117] Phlyctenular keratitis has most often been attributed to tuberculin protein. Regardless of the exciting agent, this is most likely an allergic disease. On the North American continent the incidence is highest among the Eskimos and less among the Indians.[118,119] In both groups there is a high ratio of tonsil and adenoid infection, drum and hearing abnormalities, and prevalence of chronic upper respiratory infections.

The Arthus reaction is a specific antigen-antibody reaction which is characterized by severe localized necrosis and tissue slough following repeated injections of antigen. This reaction is easily demonstrable in the skin, but a corneal reaction has been obtained only when vascularization is present. However, recently the reaction was provoked in nonvascularized rabbit corneas after repeated injections of horse serum and egg white. This suggests that corneal vascularization is not necessary for production of the reaction as previously assumed.[120] However, such a conclusion is probably not warranted, since intracorneal injections of almost any substance will stimulate superficial stromal vascularization within a few hours. Therefore, in the above study vascularization probably was present even though microscopic.[121] This rapid appearance of capillaries in the superficial stroma also suggests that channels exist in the corneal tissue which permit rapid extension of capillary buds. If this is correct, corneal edema may not necessarily be a forerunner of neovascularization, although edema probably enhances the rapidity and extent of vessel formation. Corneal neovascularization also occurs during inflammation of the iris or ciliary body in the absence of edema.[122]

In west Africa the differential diagnosis of punctate keratitis lies between epidemic keratoconjunctivitis, herpes simplex, and keratoconjunctivitis due to ocular onchocerciasis.[123] The keratitis of these three diseases have similar characteristics. Some unusual types of keratitis include a bilateral corneal inflammation after total gastrectomy for carcinoma,[124] corneal abscess following bee sting,[125] and chronic corneal edema from a grain of sand in the chamber angle.[126]

III. Degenerations

A. Dystrophies

The hereditary degenerative diseases of the cornea may best be classified as granular, macular, reticular (lattice), and atypical. This classification is not universally accepted and has the disadvantage of being based on gross morphology rather than on pathologic change. Nevertheless, it is functional. These degenerative diseases have in common a hereditary background with onset in the first decade of life. Corneal involvement is always bilateral.

Granular dystrophy is characterized by white granular glass-like opacities situated close to Bowman's membrane. There is a clear zone between the opacities and the limbus. They are slowly progressive, and visual depression occurs late. Pathologically there is alteration in the epithelium, and masses of hyaline substances separate the epithelium from Bowman's membrane. Numerous dehiscences are present in Bowman's membrane, and the nerve fibers are disrupted.[127] Macular dystrophy is characterized by diffuse progressive clouding of the cornea. Centrally the lesions are situated superficially, and peripherally they appear in the deeper stroma. Visual acuity is affected early. Reticular dystrophy is distinguished by a network of linear stromal opacities. Decrease in vision occurs early. Dystrophic changes may occur in the nerve fibers in addition to the stromal alterations.[128] Atypical dystrophy is a hetero-

genous group probably containing variants of one of the three basic types, although at least some may be new entities. The list of atypical cases is fairly large.[129] Some of the more recent cases that may be added to the atypical group are the following ones: 1. A dystrophy characterized by flat, discrete opacifications and small, bleb-like structures situated on Descemet's membrane, which extrude into the aqueous. 2. A dystrophy limited to discrete opacities of the epithelium with no involvement of the stroma.[131] 3. A bilateral stroma dystrophy that is visible only on biomicroscopy and characterized by small, sharply delineated flat spots that occur at any depth. The spots vary in size, shape, and number and are diffusely disseminated over the entire cornea. The remaining stroma is clear. Visual acuity is unaffected.[132] 4. A nonprogressive dystrophy characterized by irregular, sharply delineated, stromal opacities of various sizes and shapes, appearing in all layers of the cornea and most dense over Descemet's membrane. Visual acuity is not impaired. 5. A progressive dystrophy that appeared in a 3-year-old child, associated with severe subjective symptoms consisting of conjunctival hyperemia, blepharospasm, and corneal opacity. The corneal opacities became confluent and severely impaired vision. The tissue changes consist of subepithelial fibrosis and severe damage to the epithelium, with disruptions in Bowman's membrane.[133]

Primary dystrophies of the cornea have also been noted in association with abnormalities of the iris.[134] These dystrophic changes may involve ectodermal tissues as well as mesodermal. Salzmann's nodular dystrophy is essentially an acquired dystrophy following local ocular disease.[135] It is most often unilateral but may be bilateral and is characterized by the appearance of an elevated lesion on the surface of the cornea. Clinically this lesion consists of scattered milk-white, crescentric opacities. A keratitis may be followed by a mosaic dystrophy without elevated lesions, which differs in distribution from Salzmann's nodular dystrophy.[136]

Crystalline degeneration of the cornea is a rare dystrophy, probably acquired and related to a systemic disturbance.[137,138] It may represent a variant of lipoid degeneration. Crystalline salts are scattered throughout the whole thickness of the peripheral corneal parenchyma. The central zones are clear. This disease is to be differentiated from cystinosis. Primary lipoid degeneration of the cornea is a rare dystrophy characterized by dense yellowish fatty infiltration of the entire thickness of the stroma.[139] Crystalline deposits may appear in the superficial layers. The disease is progressive, and ultimately the visual acuity is impaired. The fatty deposition may be related to increased blood cholesterol. Subepithelial calcium deposits occur in prolonged hypercalcemia which may ultimately reduce visual acuity.[140] This deposition is reversible with control of the hypercalcemia. Dermochondrocorneal dystrophy involves multiple systems and is characterized by postnatal development of osteochondral deformities of the hands and feet.[141] Later there is degenerative change in the skin, and finally corneal opacities develop. These consist of subepithelial, superficial central opacities which vary in size and shape. The density increases, and ultimately visual acuity is impaired.

Marginal corneal dystrophy is of unknown origin and is characterized by loss of stromal substance in the periphery.[142] A groove paralleling the limbus appears within the clear cornea, and a marked thinning occurs at the base of the groove. The disturbance can be either unilateral or bilateral. Ultimately corneal ectasia occurs with severe reduction in visual acuity.[143,144] Spontaneous rupture can occur. Although the etiology is unknown, it has been related to bacterial infection.

Primary epithelial and endothelial dystrophy of the cornea is relatively common and accounts for a significant percentage of visual loss in the older age groups. Endothelial degeneration is probably the pri-

mary site of involvement, for as long as the endothelium is sufficiently intact to maintain proper hydration of the cornea the changes in the stroma and epithelium do not appear. Stromal hydration and epithelial degeneration are secondary to the endothelial damage. The most characteristic changes are in Descemet's membrane and endothelium.[145,146] The endothelial nuclei vary in size and shape and are distorted by globular bodies of different sizes. The globular bodies on Descemet's membrane may be intracellular cytoplasmic bodies of low density which enlarge, break the cell border, and fuse. In this manner the regular pattern of the normal endothelial cells is disturbed.[147] Clinically these globular bodies are seen as nodular excrescences on Descemet's membrane. In the most advanced cases the corneal lamellae are infiltrated with fluid and are separated. Even in normal corneas endothelial cells are diminished in number with advancement of age.[148]

Keratomalacia may be considered an acquired dystrophy primarily involving the epithelial layers, with ultimate involvement of the stroma. This type of degeneration is related to a deficiency in nutritional factors, particularly vitamins.[149,150] In the keratinizing epithelium of vitamin A-deficient mice, keratohyalin granules are most prominent in the superficial layers of the epithelium and absent in the basal layer.[151] Similar changes appear in other mucous membranes. In the process of cornification the cells of the epithelium become flattened and loosened from the layer beneath, with consequent loss of nuclei. Studies with the electron microscope suggest that the basic alteration is due to a disturbance in the cellular metabolism, which is expressed by production of keratohyalin granules. Production of the keratohyalin granules may be related to degenerative changes in the mitochondria. Protein deficiency may also be a factor in the pathogenesis of keratomalacia, and such a deficiency may often accompany vitamin A deficiencies.[152,153] Keratomalacia may also occur as a congenital defect.[154]

In keratoconus the pathologic changes are related to atrophy and degeneration of the central corneal stroma. The ectatic cone follows loss of tensile strength of the stroma, and the epithelial changes undoubtedly are secondary manifestations.[155] The pathogenesis of keratoconus and the posterior scleral ectasia of high myopia may be similar.[156,157] The precise mechanisms involved are not known, but in keratoconus there is some suggestion that endocrine dysfunction is a factor.[158,159] Intraocular pressure is not a primary factor.[160]

B. Tumors

Carcinoma in situ (Bowen's disease) is a malignant degeneration of the conjunctival and corneal epithelium which has not extended beyond the limits of the basement membrane. The tumor is fairly common in elderly persons, and its development is usually preceded by chronic irritation with subsequent hyperplasia. Microscopic examination shows proliferating pegs of basal cells. The cells vary in size, shape, and staining characteristics and show loss of polarity. Tumor giant cells and mitotic figures are common.[161] An inflammatory reaction is usually present in the substrate, while is often characterized by a lymphocytic proliferation. Epithelial plaques may constitute an earlier stage of transition from the benign to the malignant.[162,163]

Treatment is variable. Simple excision is probably the most commonly chosen procedure. However, diathermy coagulation is safe and effective.[164] Irradiation is also advocated, although the effectiveness of this type of therapy is somewhat controversial.[165] Lamellar keratoplasty has been performed with success.[166,168]

When the malignant growth extends beyond the confines of the basement membrane and invades the adjacent tissues, it may be considered a frank squamous-cell carcinoma. These tumors are prone to grow slowly but will invade and destroy the corneal and scleral stroma. They usually respond well to irradiation but may be adequately treated with simple excision or

simple excision and keratoplasty. If they become too extensive, enucleation or exenteration is required.[168,169]

In some respects precancerous melanosis is analogous to Bowen's disease, since they are both carcinomas in situ.[170,171] Both ultimately extend beyond the limits of the epithelium to invade adjacent structures. They precede malignant melanoma in one instance and squamous-cell carcinoma in the other. Primary malignant melanomas of the conjunctiva and cornea are exceedingly rare, and they may arise from preexisting benign nevi.[172-174] Malignant melanomas of the cornea and bulbar conjunctiva have usually been considered as highly malignant. However, this attitude is probably incorrect, since long survival is not uncommon in the small series available for study.[175] However, tumors are prone to recur locally in spite of repeated excision.[176] When the tumor is small the treatment of choice is local excision. Diathermy coagulation has also been advocated.[178]

Nevoxanthoendothelioma is a histiocytic tumor occurring predominantly in the skin and occasionally elsewhere, including the eye. It is almost exclusively limited to infants and children. In previous reports the ocular lesions have appeared on the iris. However, the tumor may occur on the external surface of the globe, such as the limbus.[178]

Of the benign tumors of the cornea and conjunctiva, pterygia are probably the commonest and often the most difficult to manage. Since the pathogenesis of this lesion is not understood, treatment to date has been largely empirical. This lesion is commonest in hot dusty environments. This suggests that it may be a nonspecific tissue response to repeated insults from chronic irritation. There is some evidence relating pterygia to other disturbances of the lids and ocular adnexa, such as Meibomian concretions, inflammatory granulations, roughness of the lid margin, and chalazia.[179] Excessive exposure to ultraviolet light may be a causative factor in the development of these diverse lid abnormalities and, therefore, only indirectly responsible in the genesis of pterygium. It is difficult to conceive of a virogenic origin, as has been suggested,[180] because of limitations in anatomical distribution of this lesion. Neither of the above explanations accounts for the rare appearance of congenital pterygium.[181]

Several methods of surgical treatment for simple pterygia are available, most of which are effective. Most often simple excisions or transplantations are employed.[182,183] However, the problem of recurrent pterygia is more difficult. Excision and postoperative irradiation is most often effective but not without hazards. Mucous membrane grafts from either the buccal surfaces or elsewhere on the globe may be sufficient.[184,185] However, these grafts are easily reinvaded with neovascular tissue, and the incidence of recurrence is appreciably higher than by other methods. Lamellar keratoplasties are very effective.[186] The rationale for this procedure appears to be excellent. Since the lesion is basically a disease of the corneal stroma, it appears logical that replacement of the diseased tissue by new stroma should eliminate the tendency for regeneration. A unique and supposedly effective method consists of excision of the pterygium followed by a keratome incision into the anterior chamber transecting the path of the lesion. The resulting scar and section of a hypothetical trophic nerve is thought to inhibit the tendency to revascularization.[187] There is some difference of opinion regarding the effectiveness of irradiation, but when applied it is most effective postoperatively.[188,189]

IV. Surgery

A. Wound Healing

Of the many factors involved in the genesis of a corneal scar, one of the more controversial relates to the origin of the cellular elements involved. Hypothetically, tissue reaction to injury and repair should parallel similar reaction occurring elsewhere and should be modified only by the environment in which it occurs. When soft

tissues are injured, chemotactic substances are presumably released from damaged cells, stimulating an inflammatory reaction. This is characterized by an influx of polymorphonuclear leukocytes from the peripheral blood stream, macrophages from the blood stream and adjacent tissues, lymphocytes, and fibroblasts. These cells are all of mesodermal origin. However, in corneal wounds there are differences of opinion regarding the origin of these cells. The controversy hinges largely on the ability of adjacent corneal cells to undergo transformation from one type to another (metaplasia). For example, from studies of experimental wounds, stromal cells are thought by some to be capable of metaplasia to leukocytes, lymphocytes, and fibroblasts, and epithelial and endothelial cells are capable of transition to fibrocytic tissue.[190-192] However, the concentration of leukocytes in traumatized stroma in aleukemic animals parallels the reduced white cell count. This suggests that these cells must originate from the blood stream, since leukemia should have no effect on inflammatory cells if they arise by metaplasia.[193] When flat preparations of the cornea are examined microscopically, the stromal cells appear to be long and have many straight processes. These processes intertwine to form a syncytium, and the spaces between are filled with regular layers of corneal lamellae. After injury, cellular changes occur rapidly. The stromal cells lose their long, straight processes and their interconnections. Some degenerate, but surviving cells assume short-branched formation. These altered stromal cells are capable of migrating into the area of injury and bridging the defect. Invading lymphocytes and leukocytes are also present, but they appear to originate from the perilimbal vessels and to migrate to the area through preexisting channels in the stroma (Bowman's canals). Fibroblasts are also present, but these differ from the connective tissue cells of stromal origin and maintain a morphologic difference even in maturity. Neovascular buds extend into the cornea from the limbal vessels and do not appear to be formed from corneal stromal cells.[194] Opposite opinions regarding the origin of neovascular buds have been made.[195] On microscopic examinations of vertical sections, fibroblasts appear within the first 12 hours after injury and increase rapidly until they are too numerous to count in an oil-immersion field at 120 hours. They appear to originate first from stromal cells and later from monocytes which have migrated in from the limbus. Despite the difference in origin these fibroblasts appear morphologically indistinguishable.[196] Fibroblast activity is decreased in the absence of epithelium and does not reach a normal rate until the epithelial surface has been restored. Removal of the epithelium appears to disturb the corneal stromal cells, which the investigators feel are an important source of fibroblasts. Release of histamine at the wound site is thought by some to inhibit healing. However, induced corneal wounds treated by antihistamine are adversely affected.[197]

When endothelium is damaged, regeneration is not evident until 24 hours after injury, but by 48 hours a well-defined endothelial layer covers the defect. Regeneration occurs both by mitotic and amitotic division. The endothelium continues to proliferate until the posterior corneal gap is filled. The portion between the stromal edges is gradually replaced by fibrous connective tissue. This portion originates either by metaplasia of endothelial cells or by replacement from the stroma. Formation of new Descemet's membrane is not evident in the first three weeks, but after 90 days it is about 50% of its original thickness, after which no visible increase occurs.[198,199]

Dehiscences in the epithelium are closed by a mechanical sliding of the adjacent epithelium over the denuded surface.[200] This process is evident within one hour after injury and is later reinforced by increased epithelial proliferation. The cells will spread along any smooth surface, including crevices or cut edges, until the defect is closed. This growth characteristic of the epithelium is important to ophthalmic surgeons, since

epithelium tends to grow along fistulous tracts, suture tracts, or gaping wounds and accounts, in part, for epithelization of anterior chambers.

B. Keratoplasty

While keratoplastic techniques have become fairly well standardized, several problems of major proportions are far from solved. These include, among others, the fate and role of the various corneal tissue planes, the role of the antigen-antibody reaction in delayed clouding, and adequate prolonged storage of donor material.

Opinions differ concerning the ultimate fate of the graft, ranging from little or no replacement to complete replacement of all constituents by the host cornea. Histologic studies of successful human grafts obtained after death reveal no structural differences from normal cornea.[201,202] This is also true of lamellar grafts in experimental animals.[203] Histologic examinations at different time intervals reveal that the majority of stromal cells survive. The only pathologically altered stroma cells are those adjacent to the wound in both the donor and the host cornea. However, judging from growth characteristics alone, host epithelium must be capable of resurfacing donor tissue. Clinically this has been noted on many occasions, but it is questionable whether replacement of intact donor epithelium always occurs. Metabolic studies of host and donor tissues support the above observations. In normal corneas radioactive sulfur tagged to ground substances has a biologic half-life of approximately 32 days. In a successfully transplanted graft this radioactivity decreases to one-third of the normal value within two weeks. The elimination rate then returns to normal. This decline indicates loss of some constituent of the ground substances, probably protein and mucopolysaccharide. Similar experiments tagging the cellular structures reveal a considerably increased rate of cell death after keratoplasty. On simultaneous histologic examinations cell death and regeneration is evident but there is no change in the lamellae or Descemet's membrane. The findings suggest that ground substance and cells may be replaced in part by the host but that the stroma fibers and Descemet's membrane remain intact. Radioactive S^{35} uptake by the graft is initially reduced, but the uptake of the host cornea is also diminished in the area adjacent to the corneal wound. Recovery follows the same pattern as in the graft. The rate of synthesis of sulfomucopolysaccharides is not increased in the graft immediately after keratoplasty, despite loss of ground substance. Since mucopolysaccharides are rapidly eliminated from the graft and immediate postoperative synthesis is diminished, a net loss of mucopolysaccharides must be assumed. Apparently there is a mucopolysaccharide and protein deficit for the first few weeks after surgery.[204,205] To summarize, it appears that no replacement of stromal fibers and Descemet's membrane takes place. There is partial replacement of the ground substance and stromal cells and probably complete replacement of epithelium and endothelium.[206]

Delayed clouding of the graft has been most often attributed to an antigen-antibody reaction between the donor and host. Corneal vascularization is thought to be necessary for the reaction to take place. This concept has been supported by experiments which were designed to stimulate sensitization to penetrating corneal homografts by previous implantation of tissues in the recipient. The incidence of clouding in the sensitized animals has been higher than in controls. However, the incidence of clouding of interlamellar grafts in sensitized and nonsensitized animals shows no significant difference.[208] This discrepancy may be due to the influence of aqueous on the penetrating grafts, since aqueous appears to contain antibodies.[208,209] Ordinarily an immune reaction will destroy sensitized tissues two to three weeks after the implantation. When corneal homografts are buried in the lateral body wall of both sensitized and nonsensitized guinea pigs, an atypical reaction is observed. The cornea appears to act more like cartilage, which behaves differently

than other tissues and survives much longer. Instead of being destroyed, the corneal grafts tend to form cysts, and the epithelium of these cysts may be preserved for periods up to three months. Also the leukocytic, lymphocytic, and fibroblastic infiltration normally found in the destruction of unacceptable homografts is absent.[216] These observations suggest that corneal tissue may have very low antigenic properties. It appears that the exact relationship of antigen-antibody reaction to delayed clouding of the cornea is yet to be established.

Corneal heterotransplants have been largely unsuccessful. When chicken corneas are grafted into rabbits, clouding occurs. However, when the chicken cornea is stored in rabbit serum for three days prior to transplantation, some success is attained.[213] Avian corneas appear to be better tolerated in rabbit eyes than mammalian corneas by lamellar and interlamellar methods. There is a possibility that a phylogenetic relationship exists, and the further apart the donor and recipient are phylogenetically the less likelihood of donor-recipient reaction.[214] The corneal epithelium may also be an influence. In a small series of laboratory animals a larger number of successful homografts was obtained when the host epithelium had been removed.[215] Tissue reaction to interlamellar grafts is also greater when the epithelium is attached.[216]

Long-term storage of corneas still remains a problem and to date has not been adequately solved. Probably 15% glycerin (glycerol) and saline is the best medium now available. Glycerin apparently protects the corneal tissues from the harmful effects of freezing and thawing.[217] Glycerin-frozen corneas maintain their viability over three months, and the stored grafts may remain clear indefinitely.[218] The relationship of viability to temperature appears to be significant. Corneas stored at 4 C reveal much greater protein degeneration than corneas stored below 0 C.[219,220] In low freezing temperatures degradation of both nuclear and cytoplasmic nucleic acids is reduced.[221] The pH of the storage solution is also a factor. Endothelial viability is maximum at pH 8.8, although oxygen uptake is still reduced.[222] Successful grafts have been obtained in humans after (1) short-term freezing of the donor cornea,[223,224] (2) storage in glycerin for as long as nine months,[225] and (3) short-term storage in a solution of intradex, dextrose, phenol red, chloramphenicol, streptomycin, and nutrient agar.[226] A lyophilized cornea is one that is dehydrated under a vacuum and kept hermetically sealed. This method of storage has promise and has been used successfully in lamellar keratoplasties.[227]

While present surgical techniques are fairly well standardized, suggestions for refinement frequently appear in the literature. In an effort to reduce the incidence of lens injury, trephines have been devised which prevent too great a penetration and loss of the anterior chamber on entry into the eye.[228,229] Postoperative air injection into the anterior chamber has been suggested as a means of reducing the incidence of glaucoma.[230] This may also reduce excessive hydration of the graft by physical separation of the two media. Better protection of the graft surface may be obtained by installation of a rubber condom.[231] The membrane may have the additional advantage of improving fixation.

The scope of keratoplasty as effective therapeusis has not yet been fully exploited. Penetrating grafts have been employed successfully for intercalary staphyloma,[232] perforated corneal ulcer,[233] and corneal dystrophies.[234] Lamellar grafts have been employed with success in chronic corneal ulcers,[235,236] chronic herpetic keratitis,[237,238] ophthalmoblennorrhea,[239] recurrent pterygia,[240] and marginal corneal dystrophy.[241] Total penetrating grafts remain hazardous but may be of tectonic value.[242]

V. Pharmacology

Inhibition of wound healing is often considered an undesirable side-effect of local and systemic steroid therapy. In corneal wounds, at least, this inhibitory effect may be negligible. Also, factors other than ster-

oids may appreciably alter the progress of healing. For example, induced central corneal wounds heal less rapidly than peripheral wounds, and there is much less vascularization of the involved central site. There is some evidence that instillation of steroids does not inhibit the growth of the blood vessels, nor do steroids predispose the cornea to bacterial infection.[243] However, once infection has occurred, steroid therapy may interfere with the usual tissue defense mechanisms and allow for greater dissemination and increased intensity of the infection.[244,245] All steroids are contraindicated in the early phases of dendritic ulcer (herpes simplex),[246] but beneficial effect may be obtained in the later metaherpetic lesions, including disciform keratitis. Of the various steroids now available, fludrocortisone (fluorohydrocortisone) probably exerts the most potent anti-inflammatory effect.[247,248] Because of its severe toxic side-effects it cannot be administered systemically. However, for inflammation of the cornea and anterior segment local instillations are sufficient.

For serious ocular infections the administration of a specific medication effective against the causative organism is most desirable. Cultures and sensitivity tests provide the necessary information. This means a delay of several days even if laboratory facilities for such determinations are easily available. When it is necessary to start therapy immediately, cultures and scrapings should be obtained before administration of any antibiotic or sulfonamide, since identification of the causative agent is handicapped by therapy. In such nonspecific treatment temporary administration of a wide-spectrum antibiotic is most logical. Of the antibiotics, chloramphenicol, bacitracin, oxytetracycline (Terramycin) and erythromycin are most often used. Biomycin is effective against pneumococci, staphylococci, and streptococci.[249] Oleoandomycin is a new antibiotic which inhibits Gram-positive bacteria but has little effect on Gram-negative bacteria, Rickettsia, or larger viruses.[250] It has a spectrum equivalent to erythromycin but less than chloramphenicol and the tetracyclines. The drug is severely toxic when injected subconjunctivally. A locally administered tetracycline (Achromycin) is effective for tetanus, as are the other tetracyclines and penicillin.[251] Chloramphenicol was found to be the only effective agent for a corneal graft severely infected with Gaffkya tetragena (Micrococcus tetragenus).[252]

For allergic inflammations of the cornea and conjunctiva, steroids plus an antihistaminic preparation may be superior. A metisteroid-antihistaminic drop (Metreton) is effective in reducing ocular inflammations and edema associated with allergies, including vernal conjunctivitis. However, a superiority of the combination over the steriod alone has not been established.[253,254]

Local administration of steroid is probably the most effective treatment for interstitial keratitis.[255-257] Of the steroids available, hydrocortisone may be superior. Treatment should be combined with systemic treatment of syphilis.[258,259] While local administration of these drugs is effective for inflammation of the anterior segment of the eye, they do not affect progressive destructive lesions involving the posterior segment.[260]

Superficial corneal opacities, particularly after trauma, may be beneficially affected by subconjunctival injection of hyaluronidase.[261,262]

The treatment of Sjögren's keratoconjunctivitis remains unsatisfactory. Some benefit has been observed following administration of cocarboxylase and hormonal therapy.[263,264] Transplantation of Stenson's duct may give relief.[265] However, local administration of artificial tears probably remains the common treatment of choice.[266]

Prompt debridement of damaged corneal and conjunctival tissue without grafting may be advisable for chemical burns. This has the advantage of removing the offending agent, which may have impregnated the tissues, without introducing newer complica-

tions or hampering recovery.[267] Debridement and simultaneous grafting of mucous membranes is also advocated.[268] Subconjunctival injections of a mixture of the patient's blood and penicillin may hasten reepithelization of the cornea and regeneration of cells.[269]

Cyclonine hydrochloride (4-N-butoxy-β-biperidinopropiophenone hydrochloride) is a topical anesthetic with inherent bactericidal and fungicidal activity particularly when coupled with chlorobutanol.[270] Cornecaine (*p*-propyl-amino-benzoic ester of diethyl-aminopropandiol) is a well-tolerated topical anesthetic that is approximately seven times more active than cocaine.[271] While the drug is not tolerated by subconjunctival injection, it is only slightly irritating when applied topically. It has little or no toxic effect for corneal epithelium. Sympocaine hydrochloride is a topical anesthetic of low toxicity which is not irritating when instilled into the conjunctival sac.[272] Its anesthetic properties compare favorably with tetracaine (Pontocaine). In general, anesthetics lose their effectiveness after prolonged administration. They are frequently toxic to the corneal epithelium and tend to inhibit regeneration. This toxic effect may be enhanced when administered in the form of ointments.[273] Of the various available topical anesthetics, Metacaine (piperocaine 2%) and Xylocaine (lidocaine 2%) are probably the least noxious.[274]

In order for irradiation to be effective it must be absorbed by the tissues being treated. Hence, high-energy radiations which pass through tissues and are absorbed at greater depths serve little purpose. β-radiation has low penetrating power and is best applied to superficial lesions. It acts by damaging the cell nuclei through ionization, and when sufficiently concentrated it can bring about the death of the cell.[275] This therapeutic measure should probably be limited to those conditions that do not respond well to other measures.[276] Undesirable side-effects include telangiectasis, keratinization of the epithelium, atrophy of the sclera, superficial punctate keratitis, corneal vascularization, scarring, and radiation cataract.[277] With low-voltage radiation, such as β-radiation, opacities may be limited to sectors without general involvement of the lens. Corneal clouding associated with epithelial bullae, vesicles, and loss of sensitivity may be a delayed manifestation of irradiation.[278]

Low-voltage x-ray has been reported as effective for epibulbar malignant melanomata,[279] vernal catarrh, superficial vascularization, hemangiomata, and papillomata.[280,281] There is some difference of opinion concerning the advisability of irradiation for pterygium. It is probably most effective when applied postoperatively.[282]

Exposures to a variety of organic solvents, including xylol, toluene, sulfur gases, various acids and alkalis used in dyes, and ethyl and butyl acetates, induce corneal and conjunctival irritations, most of which are superficial and reversible. Punctate defects are common in the cornea and are accompanied by mild photophobia, conjunctival hyperemia, and, occasionally, anesthesia of the cornea.[283-285] Caustic burns may occur from introduction of products used for cleaning rust stains, particularly products containing metallic fluoride.[286] Chronic dermatitis of the skin of the hands, lids, and conjunctiva occur in medical workers handling streptomycin.[287] Characteristic corneal lesions have been observed in workers engaged in the manufacture of hydroquinone.[288] A dark stain appears in the conjunctiva and cornea of these workers because of precipitation of brown pigment granules within the tissues. The long-range effects of exposure to this chemical is more serious because of structural alterations that appear in the stroma. A high degree of astigmatism may develop with alteration of the corneal curvature, simulating some of the characteristics of keratoconus. Chloroquine is an antimalarial drug that has been found effective in the treatment of rheumatoid arthritis. The drug has few toxic side-effects, although a blurring of vision

has been occasionally noted. Nevertheless, corneal changes do occur which consist of alterations in the epithelium. The early alterations appear as an irregular curved withish line in the epithelium below the level of the pupil. In more advanced lesions, these deposits are yellow.[289] Blurring or mistiness of vision occasionally occurs. These effects usually disappear with discontinuance of the drug. Phenylbutazone (Butazolidin) is another antirheumatoid drug which may induce vascularization of the cornea.[290]

Introduction of even minute amounts of detergents or wetting agents into the anterior chamber during surgery increases the incidence of postoperative striate keratopathy. The detergent may enter the eye from contact with instruments soaked in wetting agents preoperatively.[291]

VI. Sclera

Traumatic scleral tears or ruptures may be masked by an undisturbed overlying conjuntiva. When suspected, an exploration and attempted repair is always indicated, since prolapse of uveal tissue is not infrequent.[292] This type of tear most often occurs in the anterior segment, but with severe contusion the posterior wall may rupture. These ruptures are detectable with ultrasound equipment.[293] Echos from the site of perforation are reduced. Ordinarily scleral rigidity is not appreciably altered by tonography, although it is variable in both normal and diseased eyes.[294] Scleral rigidity is decreased in high myopia and after diathermy and scleral resection.[295] The reduction in scleral rigidity in high myopia is probably due to a deficiency in the formation of connective tissue fibrils of the sclera. Electron microscopy of collagen fibers in myopic staphylomata reveals an appreciable reduction in the size of the fiber. The fibers are narrower than normal and more widely spaced.[296] Other ocular changes following scleral resection include corneal hypoesthesia[297] and changes in corneal curvature.[298]

Scleral plaques occasionally observed in the palpebral fissure area of elderly persons are often referred to as hyaline plaques. They appear as punched-out, dark areas anterior to the insertion of the recti muscle. These plaques are composed of calcium sulfate (gypsum) and not hyalin.[299] Apparently this type of tissue deposition of calcium sulfate is peculiar to the sclera. Scleromalacia perforans related to rheumatoid arthritis is frequently distinguished from perforating scleromalacia following necroscleritis. The rheumatic variety of scleromalacia perforans differs from the nonrheumatic variety by the absence of inflammatory reaction and long-standing arthritis. It is doubtful that such a distinction is valid.[300,301] Scleritis and episcleritis are frequently considered metastatic from systemic disturbances. However, the reverse can also be true; metastatic infections to other organs may originate from scleral infection.[302] Scleritis is frequently resistant to medical therapy. Repeated applications of fractionated doses of radiation may prove beneficial in resistant problems, provided they are not of tuberculous origin.[303] A significant increase in uptake of radioactive phosphorous may occur with scleral granulomas from brawny scleritis, which can be confused with neoplasms.[304]

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Correspondence

CORNEAL DONOR SELECTION BY BLOOD TYPE

To the Editor:—Having read the important paper about "Corneal Donor Selection by Blood Type," by Havener, Stine, and Weiss, A. M. A. ARCH. OPHTH. 60:443-447 (Sept.) 1958, I thought it might be of interest to mention that the first to consider the possible connection between results of corneal transplantation and blood type was Anton Elschnig (*Prag. med. Wchnschr.* 39:37-39, 1914). He suggested that in my report about 49 corneal transplantations performed by him between 1908 and 1917 this question be considered (*von Graefes Arch. Ophth.* 99: 349, 1919). At that time we considered the results of this particular study inconclusive. However, the patient who showed a clear transplant during an observation period of more than four years had blood type compatible with that of the donor, well in accord with the results reported by Havener and associates.

K. W. ASCHER, M.D.
University of Cincinnati College of Medicine (19).

VISIT TO MOSCOW EYE INSTITUTE

To the Editor:—While visiting behind the Iron Curtain last July, I was invited to visit the Helmholtz State Scientific Institute for Eye Disease, known as the Moscow Eye Institute. A Canadian surgeon accompanied me. We spent an entire day with the director, Alexander Vassilyevich Roslavtsev, examining patients and seeing the physical setup.

The U. S. S. R. has seven eye institutes, each specializing in a particular phase of eye care. The institute in Odessa carries on research in corneal transplants; the Moscow Eye Institute, the one which we visited, carries on research in glaucoma, trachoma, pediatric ophthalmology, and pathology. There are 73 other eye hospitals in Russia.

We made known our desires to visit an eye hospital upon our arrival in Russia through our interpreter and Intourist, the official travel agency. On the third day we received an invitation to visit the director at the institute.

We arrived at the hospital at about 10 a. m. by special car and interpreter, and after being properly gowned we were admitted to the director's office, where we were introduced. The director talked to us for some minutes as to our activities at home, our practice, etc., apparently to establish that I was an ophthalmologist and certified in the United States. After I apparently passed his inquiry, he gave us a brief history of his institution. After this he asked us what parts of his hospital we might like to visit.

Some of the surgery for the day had been completed, and muscle surgery was scheduled for midafternoon. First we were taken on a general tour through the hospital. The corridors were wider than ones normally found in similar institutions in the United States. They contained tables, chairs, and radios. The rooms where the patients were housed held six to eight beds end-to-end along the walls, with a small corridor in the middle. The patients slept in the rooms and spent most of their time in the hall. Here they played games at the tables, ate, read, and entertained themselves, reserving the rooms for lying down, relaxing, and sleeping.

The attendants were dressed in white gowns or coats and caps. In the operating room white masks were worn. It was difficult for me to distinguish between doctors, nurses, maids, and orderlies. Over 90% of the ophthalmologists in Russia are women. I recognized their position only by introduction.

The hospital showed many evidences of hard wear. The corridors were worn, and the furniture showed much use, but on the whole the institute was very clean and tidy. Things were very well organized. New hospitals are in the plans by 1960, but so far most of the building has been for education, factories, and housing.

The operating room set-up with assistants and scrub nurses is similar to our American system. The diathermy and cautery instruments seemed to be larger and have more handles than any I have seen in the States.

The instruments used were largely of German or Russian manufacture. Many were stamped "Caemabo B CCCP." Every conceivable type of instrument was available for use. For the first time in my life I saw an optical set-up where a slit lamp, keratometer, refractometer, and lensometer were mounted on a revolving table connected to a short straight table. The patient and examiner sat at the straight table and by a push of the hand each instrument could be rolled over on the straight table in position for examination without the operator or patient moving.

Indirect ophthalmoscopy is practiced generally, although ophthalmoscopes were available similar to our May-head type. Retinoscopy under cycloplegic and glass examinations are similar to our methods employed in the States.

I met practically all the physicians as we went from one department to another. They were very anxious for me to examine and look at the various patients. I saw several corneal transplants which looked well done, with a 5 mm. trephine section. I examined two patients with retinal separations, one done by diathermy and scleral resection and the other by diathermy alone. I saw several squint patients where recession and advancement of the recti muscles was performed.

Cataract patients showed good results after a combined operation. Sutures are being used in some cases but probably not as much as in the United States. The pathologist was very anxious to discuss this with me and, after some trouble with the interpreter, said that her findings indicated that the way to close the wound was with corneal or corneoscleral sutures.

Several uveitis patients were examined. Popular methods of treatment include elimination of the focus of infection, cortisone therapy, and fever induced with hot tea and blankets.

One patient kept following me through the corridors and finally spoke perfect English. I believe he, as most English-speaking Russians we met, was anxious to practice his English on me. He told of being imprisoned in Germany with two American fliers who over a three-year period taught him English, while he in turn taught them Russian.

We visited each research department. The glaucoma division was of great interest. Much work is being done in this field. Here four out-patient beds were reserved for glaucoma suspects. The patients slept in over night and returned to work by day. During their stay the tension was checked several times. Light- and dark-adaptation rooms were available where pressure was studied under various influences. Iridectomy seemed to be the operation of choice, at it is in much of America.

The pathological department impressed me very much. Specimens were displayed effectively in glass containers on transparent shelves in the center of the laboratory. This display reminded me of similar exhibits in the Army Institute of Pathology, Washington, D. C. The director was very proud of his electronic microtome and microscope and with a great deal of pride wished to demonstrate them to me.

Contact lenses are fitted solely by women doctors. Scleral lenses seemed to be the ones of choice, the corneal lenses being reserved mainly for dress and evening wear.

The need for glasses seems much less than in other countries. Lenses are not ordered for minor prescriptions. The patient is required to pay for the glasses, which are reasonably expensive, probably explaining the few glasses worn on the streets. Examinations are conducted by the clinics at no cost to the patient.

The doctors were very friendly and congenial and wished to talk to us about all phases of medicine, including salaries, hospital duties, and hours worked. No physician has a private practice. They are all salaried by the state, as are all of the attendants. There are no volunteer workers in the hospital. The general doctor works six hours a day; the specialists and director of the institute work five, and the surgeon works four.

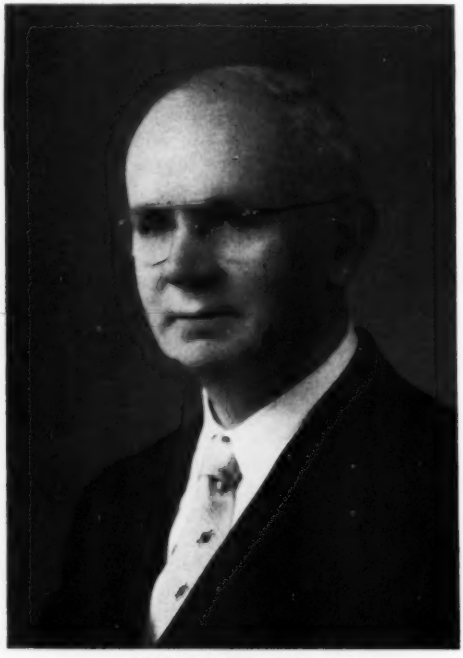
Our visit was concluded late in the afternoon, after lunch. Director Roslavtsev informed me that I was one of the first Americans to visit his hospital in many years and that he felt greatly honored by my presence.

LAWRENCE C. FISHER, M.D.
469 W. Market St.
York, Pa.

Obituaries

EDWIN FORBES TAIT, M.D.
1894-1958

Dr. Edwin Forbes Tait died at Montgomery Hospital, in Norristown, Pa., on Sept. 23, 1958. His sudden death was unexpected, even though he had not been in the best of health during the previous month. He will be greatly missed by all who were fortunate enough to know him. Dr. Tait was born in Philadelphia, on Aug. 25, 1894. He acquired his preliminary education at Philadelphia Central High School and at Brown Preparatory School. He received his A.B. degree from Temple University, in 1924 and his Ph.D. degree in physiologic optics from the University of Pennsylvania, in 1932. He also studied optics under Von Rohr at the University of Jena, in Germany.



EDWIN FORBES TAIT, M.D.
1894-1958

Dr. Tait was unselfishly devoted to the welfare of mankind. His genuine concern for the patient's welfare became manifest early in his career, when he abandoned a large optometric practice to study medicine in order that his services to his patients could be of the highest order. He matriculated at the University of Minnesota School of Medicine, from which university he received his M.D. in 1940. Since his goal from the outset was ophthalmology, he closely associated himself with that department during the four years which he spent in medical school.

After graduation from medical school, he returned to practice ophthalmology at his home, in Norristown, Pa. He became associated with the Department of Ophthalmology at Temple University Medical School, in Philadelphia, where he held the position of Professor of Clinical Ophthalmology at the time of his death. He was also Chief of Ophthalmology at Montgomery Hospital in Norristown. He was certified by the American Board of Ophthalmology. Dr. Tait was a member of the American Academy of Ophthalmology and Otolaryngology, the American College of Surgeons, the Philadelphia College of Physicians, the Association for Research in Ophthalmology, the Pennsylvania Academy of Ophthalmology, and the Pan-American Association of Ophthalmology. He was Vice President of the Pennsylvania State Medical Society, a co-founder of the National Medical Foundation for Eye Care, past-president of the Montgomery County Medical Society, and President of the Board of Trustees of the Montgomery County Medical Society. He was a co-instructor of the Home Study Courses in Ophthalmology of the American Academy of Ophthalmology.

Dr. Tait was a member of the Central Presbyterian Church of Norristown, where he was a teacher of the Men's Bible Class. He was a member of St. Paul's Lodge 481, F. and A. M., Philadelphia; Norristown Royal Arch Chapter No. 190; Hutchison Commandery, and Lulu Temple.

Dr. Tait possessed a keen intellect and an analytical mind. This was displayed in his lucid literary style, in his mathematical approach to clinical problems, and in his close conformity to the established principles of the natural sciences in his original contributions to the literature. The most notable of these was his clearly written and authoritative textbook on refraction.

Dr. Tait developed a large practice composed of truly devoted patients. He never permitted his practice to interfere with his teaching program, an endeavor which he conducted with unusual enthusiasm and success. He was esteemed by residents and staff alike because he always had the time for and the answer to their problems. His broad knowledge of all branches of optics made him at his best in refraction. Patients came from remote parts of the country to avail themselves of his skill in the difficult field of the visual aids. While his principle interests were in the fields of optics and neurophysiology of the extraocular muscles, he became a skillful ophthalmic surgeon. Dr. Tait, or Ed Senior, as he was affectionately known in the clinic, was passionately concerned about the profession's complacency toward encroachment of others on the practice of ophthalmology, a cause to which he gave more strength than he possessed. In all his varied activities his principle concern was unselfishly directed to the welfare of others. His purpose, his attitude, his ideals, and his way of life set a truly benevolent pattern, the emulation of which would profit many.

He is survived by his devoted wife, Arita E. Copp Tait, and two sons, Richard C. and Dr. Edwin C. Tait.

Ed Tait will be truly missed by his patients, his colleagues, and his family not only because he was an outstanding person and an outstanding physician but also because of his warm and pleasant personality which he so delightfully combined with an unusual degree of professional proficiency and dignity.

GLEN G. GIBSON, M.D.

News and Comment

GENERAL NEWS

Two Illustrations from Exhibit Shown at San Francisco.—The accompanying electron micrographs are from the exhibit "The Ciliary Epithelium as Seen with the Electron Microscope" by Drs. G. D. Pappas and G. K. Smelser, of Columbia University College of Physicians and Surgeons. The exhibit won honorable mention at the American Medical Association Meeting at San Francisco, June, 1958.

Plate 1.—Portions of two adjacent ciliary epithelial cells (from adult albino rabbit) showing complex interdigitations (*A*) of their boundaries. Infoldings (*B*) of the surface facing the posterior chamber (*PC*) are also shown. The surface of the epithelial cells facing the posterior chamber (*PC*) is lined with the internal limiting membrane (*I*). Zonular fibrils (*Z*) enter the internal limiting membrane but do not penetrate any closer to the epithelial cells. Elements of the endoplasmic reticulum (*ER*) as well as mitochondria (*M*) are evident in the cytoplasm of these cells. × 18,000.

Plate 2.—A portion of two ciliary epithelial cells from adult albino rabbit, facing the posterior chamber. Complex indigitations (*A*) of the boundary of these cells is evident. The surface of these cells is lined with the internal limiting membrane (*I*). Oblique profiles (at *O*) of the internal limiting membrane show that it is made up of condensation of zonular fibrils (*Z*). Elements of the endoplasmic reticulum (*ER*) as well as mitochondria (*M*) are evident in the cytoplasm. × 22,000.

ANNOUNCEMENTS

Gill Memorial Eye, Ear, and Throat Hospital Annual Congress in Ophthalmology.—The Gill Memorial Eye, Ear, and Throat Hospital, Roanoke, Va., will hold its 32d Annual Spring Congress in Ophthalmology and Otolaryngology and Allied Specialties, April 6-11, 1959. The following guest speakers are among those invited to attend:

Joseph P. Atkins, M.D., Philadelphia
Walter S. Atkinson, M.D., Watertown, N. Y.
Kenneth D. Bailey, M.D., Fairmont, W. Va.
William L. Benedict, M.D., Rochester, Minn.
F. Willson Daily, M.D., Roanoke, Va.
Windsor S. Davies, M.D., Detroit
Jeff Davis, M.D., New York
Surg. Gen. B. W. Hogan, U. S. N., Washington, D. C.
Bayard T. Horton, M.D., Rochester, Minn.
Wendell L. Hughes, M.D., Hempstead, N. Y.
John H. King, M.D., Washington, D. C.
T. Keith Lyle, M.D., London, England
George T. Nager, M.D., Baltimore
Robin M. Rankow, M.D., New York
Kenneth L. Roper, M.D., Chicago
A. D. Ruedemann, M.D., Detroit
Russell A. Sage, M.D., Indianapolis
Jules G. Waltner, M.D., New York
Edgar N. Weaver, M.D., Roanoke, Va.
Walter L. Winkenwerder, M.D., Baltimore

Course in Industrial Eye Problems.—Industrial Eye Problems, a four-day course in eye care and industrial eye programs, will be presented by the Institute of Industrial Health and the Department of Ophthalmology of the University of Cincinnati on March 9-12, 1959. The course will be open to physicians only, with preference given to men in active industrial practice. The objective of the course is to furnish the industrial physician with up-to-date information regarding eye care in industry.

The course will include basic principles of ophthalmology as well as the practical aspect of an industrial eye program.

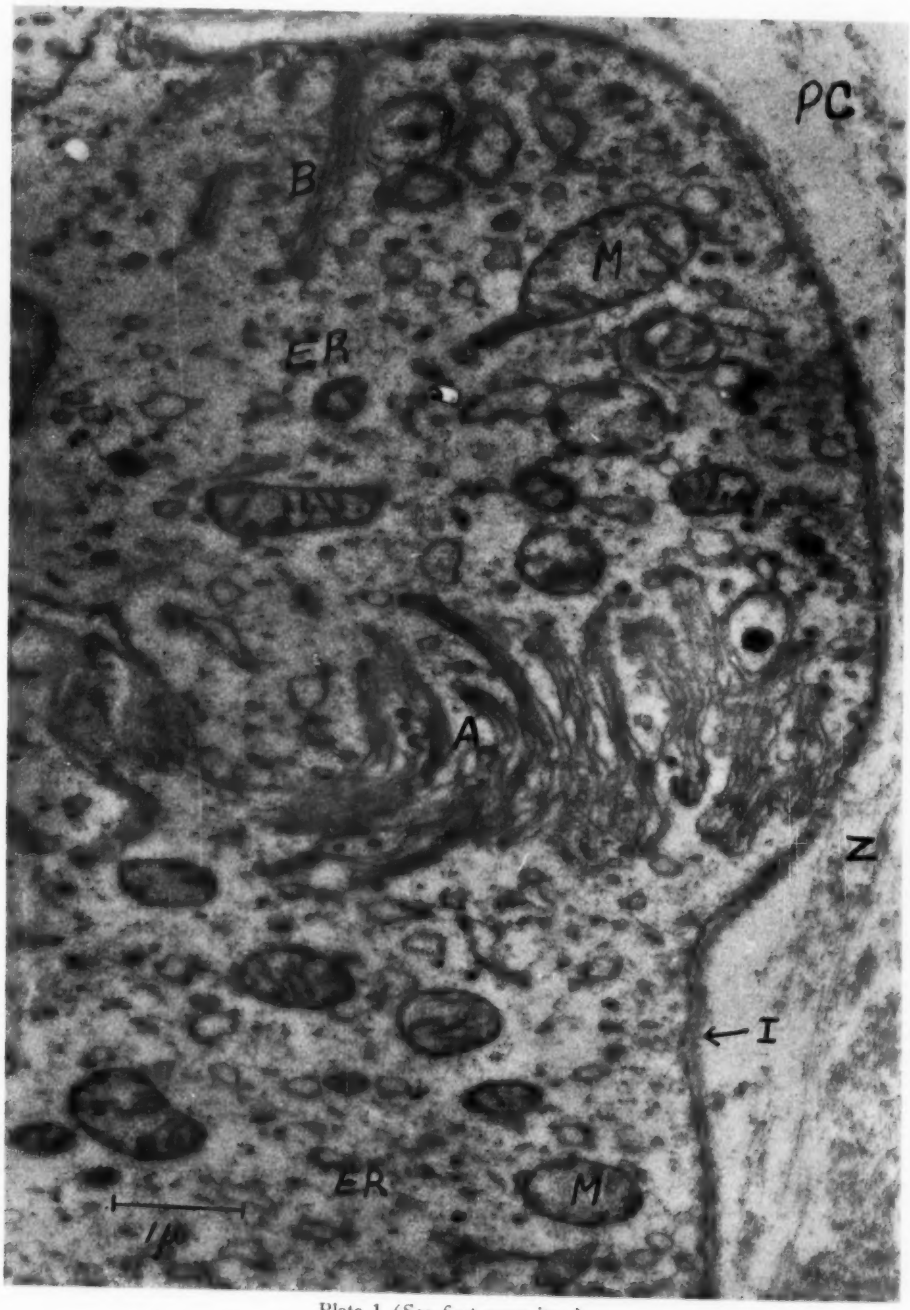


Plate 1 (See first news item)

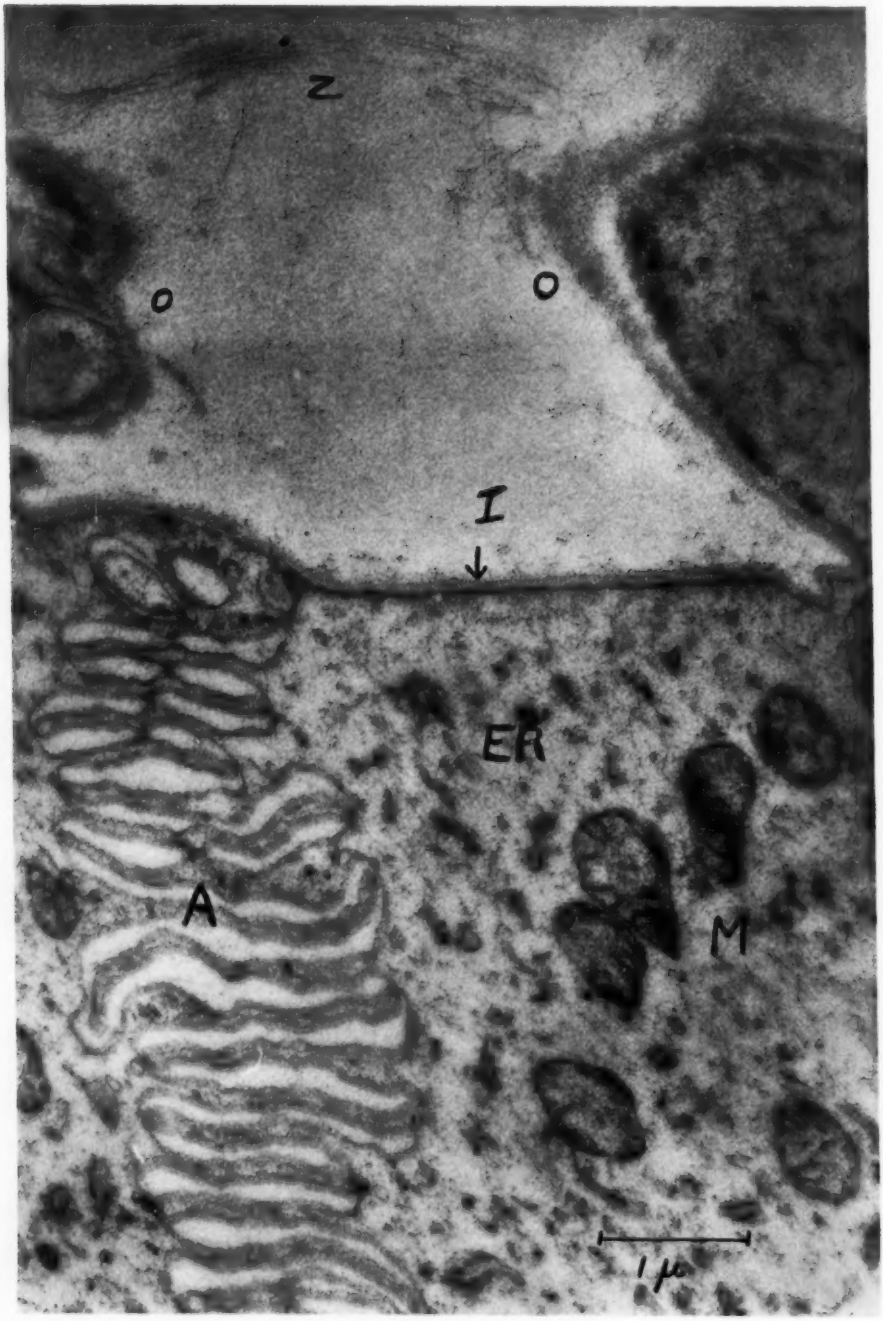


Plate 2 (See first news item)

In addition to the members of the faculty of the University of Cincinnati, guest faculty will include persons well known in the fields of ophthalmology and industrial ophthalmology.

For additional information and application, write Secretary, Institute of Industrial Health, Kettering Laboratory, Eden and Bethesda Ave., Cincinnati 19.

Annual Congress of the Ophthalmological Society of the United Kingdom.

The Annual Congress of the Ophthalmological Society will be held at the Royal Society of Medicine, 1 Wimpole St., London, W.1, on April 9-11, 1959.

The Presidential Address will be delivered by Mr. R. C. Davenport.

The subject for discussion will be "The Swollen Optic Disc." This will be opened by Dr. S. P. Meadows and Mr. D. P. Greaves. Members who wish to take part in the subsequent discussion are advised to intimate their intention before the opening of the Congress. It is emphasized that no member may speak for more than 10 minutes.

There will also be a short symposium on "The Treatment of Ocular Injuries." The speakers will include Mr. M. J. Roper-Hall and Mr. John Whitwell.

The 1959 Bowman Lecture will be delivered by Prof. Louis Paufique, of Lyons.

Courses at The Mount Sinai Hospital.—The Mount Sinai Hospital of New York, together with Columbia University, is giving the following courses: "The Use of the Schepens' Ophthalmoscope," March 10 to 26, 1959, and "Histopathology of the Eye," April 1 to 24, 1959. Complete information can be obtained from the Registrar for Medical Instruction, The Mount Sinai Hospital, 1 E. 100th St., New York.

Course in Ophthalmic Plastic Surgery.—A three-week intensive course in Ophthalmic Plastic Surgery will be conducted in New York from April 23 to May 15, 1959.

The course will consist of lectures, sessions in doctors' offices, preliminary and follow-up cases that are operated on during the time of the course, moving-picture demonstrations of various ophthalmic plastic procedures, observation and assistance at the operating table on actual surgical cases, cadaver work, and lectures and demonstrations, and ancillary subjects, such as photography, pathology, and x-ray and radiation.

The course will be limited to eight students and will be given at the New York Eye & Ear Infirmary, Manhattan Eye, Ear & Throat Hospital, and the Hempstead General Hospital. The fee will be $250.

Anyone interested should contact the Registrar of the New York Eye & Ear Infirmary Post Graduate School or any of the following persons: Dr. Wendell L. Hughes, Hempstead, N. Y.; Dr. Byron C. Smith, New York, or Dr. J. Gordon Cole, New York.

Annual Meeting of Oklahoma City Academy of Ophthalmology and Otolaryngology.—The annual spring meeting of the Oklahoma City Academy of Ophthalmology and Otolaryngology will be held March 12 and 13, 1959. The guest lecturers in ophthalmology are Dr. Michael J. Hogan, of San Francisco, and Dr. Ralph O. Rychener, of Memphis, Tenn. The guest speaker in otolaryngology will be Dr. Ramon del Villar of México, D. F. For further details communicate with Dr. E. Norris Robertson Jr., 301 N. W. 12th St., Oklahoma City.

University of Michigan Annual Ophthalmology Conference.—The annual Ophthalmology Conference at the University of Michigan will be held April 20-22, 1959, under the direction of Dr. F. Bruce Fralick, Chairman of the Department of Ophthalmology.

Applications may be addressed to the Department of Postgraduate Medicine, University Hospital, Ann Arbor, Mich.

Postgraduate Course in Ophthalmology at The Ohio State University.—A postgraduate course in ophthalmology will be given at The Ohio State University, Columbus, Ohio, March 2 and 3, 1959. The meetings will take place in the Ohio

Union Building. Registration and the program of March 2 will take place in the Conference Theater.

The speakers will be Drs. Paul A. Chandler, Boston; William H. Havener, Columbus, Ohio; Wendell L. Hughes, Hempstead, N. Y.; Ralph O. Rychener, Memphis, and Samuel Saslaw, Columbus, Ohio.

The program on Monday will include "Fundus Pictures of Interest," by Dr. Havener; "Lacrimal Apparatus," by Dr. Rychener; "Primary Glaucoma," by Dr. Chandler; "Management of Eye Injury," by Dr. Hughes; "Modern Antibiotic Usage," by Dr. Saslaw, and "The Future of Ophthalmology," by Dr. Rychener. The program on Tuesday will include three movies: "Save Your Sight," "The Taxpayer," "Case Closed," and "Management of Eye Injury," by Dr. Hughes; "Secondary Glaucoma," by Dr. Chandler; "Specific Reading Disability," by Dr. Rychener, and "Congenital Cataracts," by Dr. Chandler.

The registration fee is $20, and registration by mail is desirable. Address all inquiries to Dr. William H. Havener, Department of Ophthalmology, University Hospital, Columbus 10, Ohio.

Course at the University of Cincinnati.—The incidence of eye injury and the question of work ability of persons with visual impairment, as well as the initiation and management of eye protection programs, is a problem of major importance in the field of industrial medicine. The training of the industrial physician in ophthalmology and in the management of eye safety programs has generally been neglected. Though he may be an expert in the properties of various chemicals and their action on the body, though he may be familiar with the effect of trauma on other parts of the body and the proper method of treating injuries of an orthopedic nature, more often than not the problems of eye protection and eye care have not been dealt with in his course of training to any great extent. In an effort to overcome this rather obvious deficiency, The Institute of Industrial Health and the Department of Ophthalmology of the University of Cincinnati are presenting a four-day course entitled "Eyes in Industry" on March 9-12, at the University of Cincinnati.

Many of the eye problems which arise in industry are somewhat different than the problems as they are seen outside of industry. Questions of administration are not the least of the problems which arise. How shall the eye safety program be instituted and who shall administer it after its initiation in an industry? Shall the company pay for refraction when they require the wearing of safety glasses? What type of emergency facilities should be available for eye care in todays' industry? What type of examination is required and how should this examination vary, dependent upon the type of industry and the type of activity which the employee will be doing? What type of activities should be available for people with impaired vision? These are only a few of the many questions which arise in the day-to-day activity of an industrial medical department. It is in an effort to answer these questions that this course is to be presented.

All too often it has been the complaint of the industrial physician that the ophthalmologist is not truly aware of the problems of industry. The pat answer is not necessarily the correct answer, and the management of many of these problems in industry may have to be somewhat different than would seem to be the case at first glance to the physician outside of industry. The physician specializing in eye problems, the ophthalmologist, might well take a long glance at these problems in order to see whether adequate service is being rendered in and for industry and the industrial employee and whether the present methods in use in industry are actually the best methods.

Books

Clinical Neuroanatomy, Neurophysiology and Neurology, with a Method of Brain Reconstruction. By Louis Hausman. Price, $9.75. Pp. 522. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

This textbook combines anatomy, physiology, and clinical neurology as a unit, with emphasis on the knowledge gained by the newer methods of electrophysiology. It is also unique in presenting a method by means of which the student can construct his own anatomical three-dimensional replica of the brain, the basic kit for which can be obtained from the Clay-Adams Company, Inc., 141 E. 25th St., New York 10; a supplementary kit can be obtained from the author at 140 E. 54th St., New York 22.

The book cannot be used as a text of neurology, since the material is presented entirely from the point of view of anatomy. For residency training the reconstruction of the visual pathways and oculogyric pathways might be of real value and could be undertaken with this book as a guide.

Advances in Ophthalmology, Vol. VIII. Eighth edition. Edited by E. B. Streiff. Price, $16.80. Pp. 363, with 7 illustrations. S. Karger AG., Arnold Böcklinstrasse 25, Basel (available from Albert J. Phiebig, Box 352, White Plains, N. Y.), 1958.

The eighth edition of this review of current literature includes articles on diabetic vascular lesions, by Norman Ashton; the genesis of myopia, by E. Kraupa, and the biochemistry of lysozymes and its clinical significance in ophthalmology, by H. Schumacher, and a review of the literature on uveitis, by J. François and E. DeVos. The only paper in English is by Ashton.

This is an excellent review of all that is known about diabetic vascular lesions. Except for the article on uveitis the elite feature of the other manuscripts is the presentation of the material with emphasis on the subject rather than the author. When one wishes to review a subject he is usually not primarily concerned with the author in the text.

Most of the articles which appear in *Advances in Ophthalmology* are similar to those found in physiological reviews and are excellent for bringing one up to date in any one field of interest.

The Author Publisher Printer Complex. Third Edition. By Robert S. Gill. Price, $2.25. Pp. 134. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This book is designed to tell the author of scientific papers what he needs to know before he starts his manuscript: how to prepare the manuscript in the right way instead of the wrong way, how to read proof, and, finally, how to make new additions in the case of books.

The fact that this little volume has gone through three editions testifies to its usefulness. There are good chapters on the preparation of illustrations, particularly the preparation of graphs. There are also useful chapters on subjects not generally discussed, such as royalties. The book will be very useful for anyone contemplating the preparation of a manuscript or a book.

Ocular Allergy. By Frederick H. Theodore and Abraham Schlossman (with chapters by William B. Sherman and Robert S. Coles). Price, $12. Pp. 420. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This book is timely, since the relative proportion of allergic conditions seen by the ophthalmologist increases rapidly as the infectious lesions disappear. The authors have been identified with ocular allergies through their writings over a number of years and can speak with authority from their personal experiences. The chapter

on the basic principles of allergy, by William B. Sherman, Associate Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, forms an excellent review for the ophthalmologist.

The rest of the book is divided into an anatomical classification, listing the various forms of allergy encountered in the lids, conjunctiva, cornea, sclera, uvea, lens, retina, and optic nerve. The authors lay great emphasis on differential diagnosis and point out that this is most important, since treatment is very different in allergic and nonallergic diseases. They advise that corticosteroids and antibiotics be isolated and not compounded in prescriptions or proprietary preparations as is now the habit, and it is to be hoped that drug manufacturers will make note of this. Many patients have undoubtedly suffered serious damage by the development of allergy to neomycin incorporated in corticosteroid ointments and sold under a trade name. Usually the neomycin appears in very fine print on the label.

This book should have a very wide distribution to both ophthalmologists and allergists and is the most authoritative presentation of the subject at present available. It is a distinct contribution to our literature.

Systemic Ophthalmology. Second Edition. By Arnold Sorsby. Price, $25. Pp. 682, with 277 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1958.

Soon after the first edition of this book was published its reputation as an outstanding authoritative work on medical ophthalmology was built from the laudatory reviews which appeared in our journals. While some chapters were not as good as others, which is invariably the case in texts of multiple authorship, the general level was high, and in those subjects which were given adequate documentation one could always count on an excellent treatment of the subject.

In this new edition some of those subjects which had not received adequate coverage before are now brought up to date. While much that is new has been added, the book has been tailored to keep it down to its original size. The only objection which can be raised is to the relegation of a selected bibliography to the back of the book where it is difficult to locate.

The Psychology of Medical Practice. By Marc H. Hollender. Price, $6.50. Pp. 276. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

There are several chapters in this book which are of interest to ophthalmologists in that they pertain to the general practice of medicine in all fields. These have to do with the doctor-patient relationship. Since many of our problems are now chronic ones, such as senile macular degeneration, too much emphasis cannot be laid on just how the physician should handle patients over a long period of time with decreasing sight. Frequently, adjusting the patient to his condition is the chief function of the physician, and any ophthalmologist who fails in attempting to do this should not take care of these patients. The major portion of this book concerns fields which are not directly related to ophthalmology, although the chapter on surgical patients will be of benefit.

Therapeutic Heat. Edited by Sidney Licht, M.D. Price, $12. Pp. 466. Elizabeth Licht, 360 Fountain St., New Haven, Conn., 1958.

Of interest to ophthalmologists in this book on the therapeutic use of heat is the chapter by Louis Daily and Ray K. Daily on "Heat in Diseases of the Eye." There is no question that heat is a valuable therapeutic agent in inflammatory conditions of the uveal tract and in recent years has been forgotten in the zeal for antibiotic and corticosteroid therapy. As the authors point out, few references to the application of heat medically for ocular disease can be found in recent medical literature.

In addition to the local heating of tissues by dry and moist hot packs, the authors discuss diathermy, microwaves, infrared radiation, and the elevation of the eye temperature by febrile reactions induced by artificial-fever therapy.

This is a useful and valuable summary of a therapeutic agent which should be more frequently used.

Ophthalmic Fitting and Adjusting. By Frank Kozol, O.D. Price, $6.50. Chilton Company, 56th and Chestnut Sts., Philadelphia 39, 1958.

This is a clear and concise description of the fitting of spectacle frames. The line drawings showing the position of the frame and the instruments for changing the curvature of its various parts are well executed and should be valuable to ophthalmologists who dispense their own glasses.

The book does not encroach on any of the fields of ophthalmology.

So You Have Glaucoma. By Everett Viers. Price, $2.75. Pp. 64, with 9 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1958.

Every patient, when told he has glaucoma, has a multitude of questions to ask, either immediately or at least on the next visit after he has talked the situation over with his family. This book should be a help to the ophthalmologist in preparing the patient to ask questions which are more intelligent. Most books of this character do well until they come to treatment. This seems to be an exception, and even this portion of the book has been fairly presented, so that the average patient can hardly misinterpret whatever advice is given to him.

Stereoscopic Atlas of Human Anatomy: Section IV. The Thorax. By David L. Bassett. Price, not given. Sawyer's, Inc., Box 490, Portland 7, Oregon, 1958.

Another section of this beautiful series of stereoscopic pictures taken from the sections by Dr. Bassett, with the color photography by William Gruber, covers the thorax.

While this does not have an immediate appeal to the ophthalmologist, it should be in every library where anatomical data may be sought for. This maintains the same standard of excellence of the previous volumes.

Le Eteroforie. By Carlo Toselli. Price, Lire 6000. Pp. 287, with 28 illustrations. Casa Editrice Libraria, Rosenberg and Sellier, Via Andrea Doria, 14, Turin, Italy, 1957.

The student of ocular motility will welcome this complete review of the heterophorias, based upon a bibliographic point of view. The author presents a full and well-documented survey of the physiology of ocular motility and a complete clear picture of the various forms of heterophoria, with special attention to the hyperphorias and the less common types (insufficiency of divergence, anisophoria, etc.). The work ends with a brief chapter dealing with prisms and the prismatic action of decentration of lenses.

This monograph offers a generous panorama of the world literature on heterophoria, extending to the end of 1956.

Instruction Book for the Ophthalmologist's Office Assistant. By Carl Vellhagen. Price, DM 29.20. Pp. 207, with 108 illustrations. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig C. 1, 1958.

This compact little book in German is intended for the nonmedical assistant in the ophthalmologist's office or hospital. It outlines the anatomy and physiology of the eye in a brief but lucid fashion. Considerable space is given to functional testing, including orthoptics and field-taking. There is even a short section on photography of the eyegrounds and the anterior segment of the eye. It should be a useful little book for those office assistants who read German fluently.

Eye Surgery. Third edition. By H. B. Stallard. Price, $18. Pp. 899, with 671 illustrations. The Williams & Wilkins Company, Mt. Royal and Guilford Aves., Baltimore 2, 1958.

The third edition of this very popular book keeps to its original purpose of describing operations which the author personally uses. The unique feature of the text is the original drawings by the author. These need no apology such as he has suggested by the preface. By virtue of the fact that he knows just what he wishes to show the reader, the author can, if he has reasonable artistic skill, make a better illustration than most professional artists, and Stallard's drawings are excellent from both this and the artistic point of view.

The Eye. By E. Howard Bedrossian. Price, $11. Pp. 340, including index, with 52 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

This is a condensation of useful information from textbooks, periodicals, and the author's own lecture notes covering the field of ophthalmology. For those who desire information condensed in one-two-three order this book will have immediate appeal. It should be useful to those who are reviewing for examinations, particularly the basic science chapters—those on anatomy, physiology, and optics being particularly well done.

To abstract the diseases of the eye into one-two-three order is not very useful, and is boring to read. Further, the lack of any illustrations of disease conditions is a serious fault. The only colored illustration in the book is Reese's plate of the various stages of retrolental fibroplasia, which at this date could be well dispensed with.

Pathologie des Auges. Second edition. M. Radnot. Price, not given. Pp. 239, including index, with 285 illustrations. Hungarian Academy of Sciences, Budapest, 1958.

The second edition of this book on pathology testifies to its excellent reception by the German-reading ophthalmological world. The text is divided into an anatomical arrangement of material and considers the histological pathology of the eye and its adnexa. The illustrations are excellent, and the German is fairly easy reading. There are some particularly good correlations between ophthalmoscopic observations and histopathology, particularly in the case of cystic degeneration of the retina.

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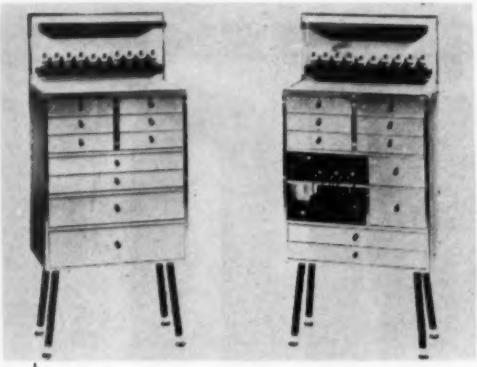

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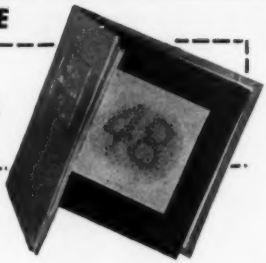

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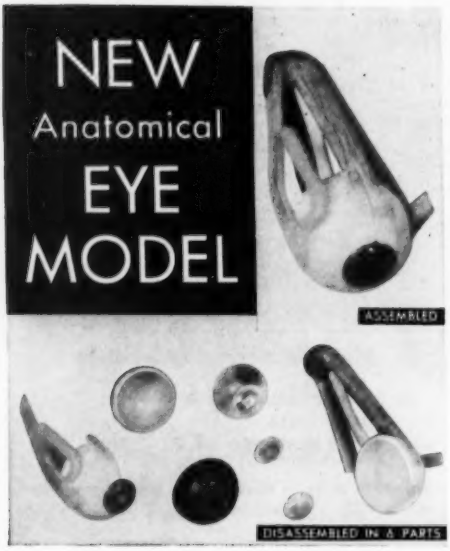

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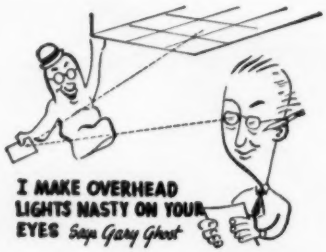

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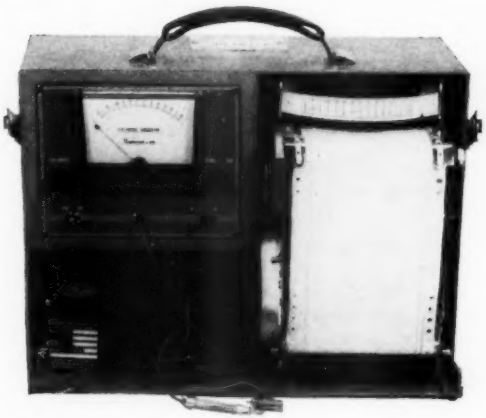

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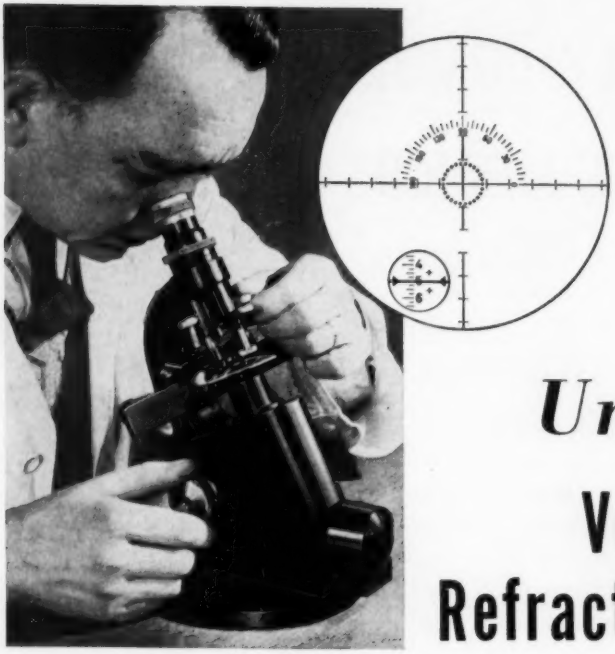

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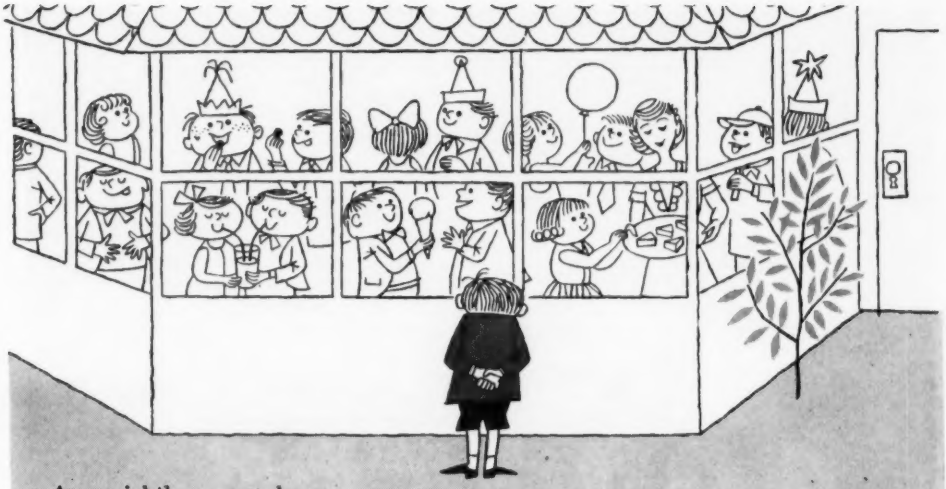

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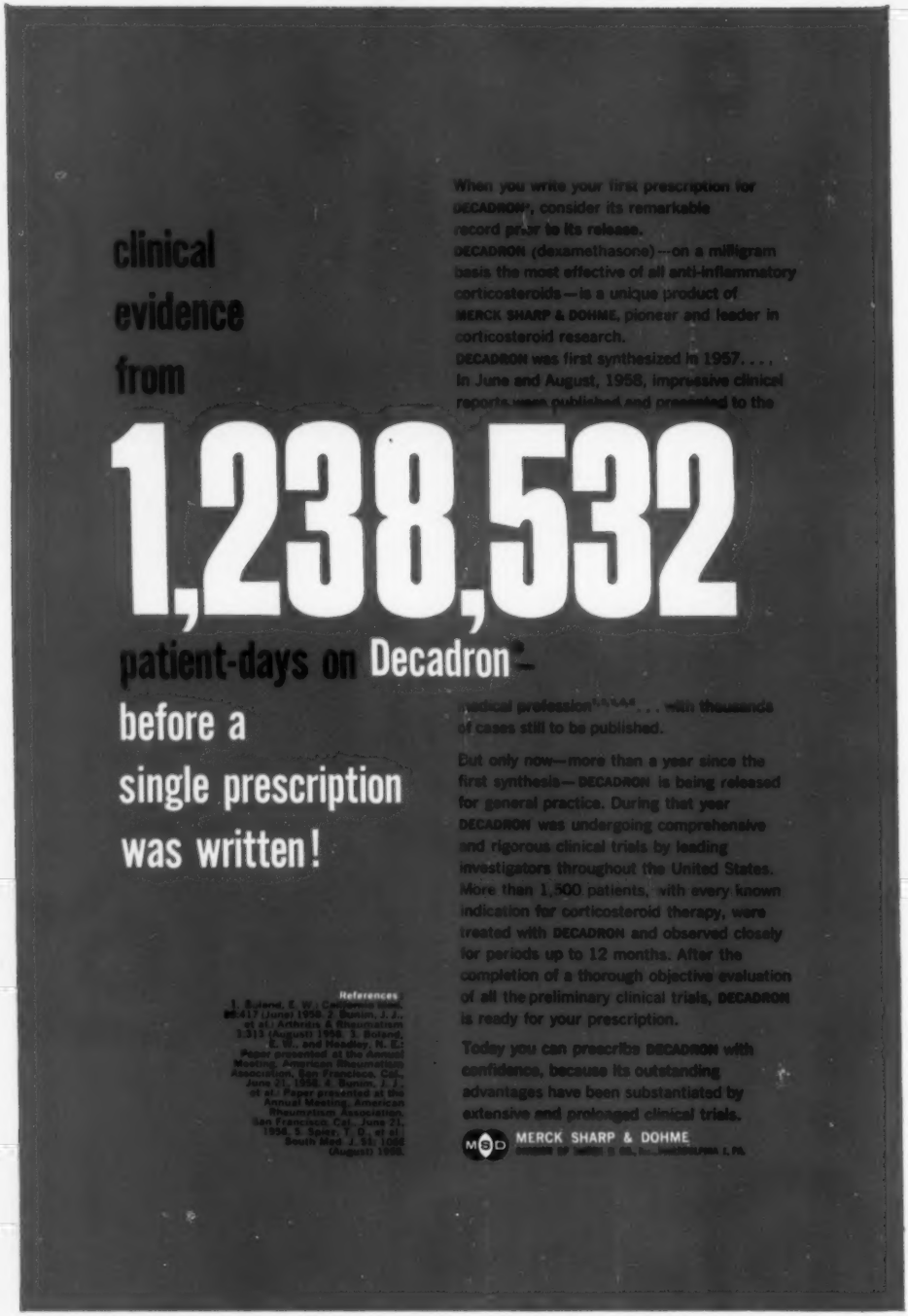
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One 4 mg. tablet of	One 5 mg. tablet of	One 20 mg. tablet of	One 25 mg. tablet of
methylprednisolone or triamcinolone	prednisolone or prednisone	hydrocortisone	cortisone

SUPPLIED: As 0.75 mg. scored pentagon-shaped tablets. Also as 0.5 mg. tablets, to provide maximal individualized flexibility of dosage adjustment, since many patients achieve adequate control even on lower dosage.

Detailed literature is available on request.

*DECADRON is a trademark of Merck & Co., Inc.
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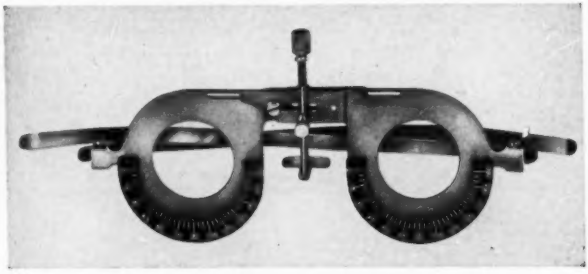
GRIFFITH-ROGERS TRIAL FRAME



This trial frame is a simple but sturdy and easily adjustable frame that is designed for rapid routine examinations over a long period of time. It will stand hard usage. Interpupillary distance is adjustable by means of a rack and pinion and the bridge height is adjusted by the same knob. Bridge may be locked. Temples are of spring steel to support the frames in position. Protractor is black with white letters and there are two front and one rear pairs of slots for the trial lenses.

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Stop for just a moment and take a careful look around. If it's time for a change, you should be certain to see American Optical's professional ophthalmic equipment with its exclusive "American Beauty" styling. Its contemporary lines and soft rich colors, Ivory Tan, Jade Green, and a lovely shade of Coral, combine with traditional AO precision and quality to offer you unsurpassed value.

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for local relief
of glaucoma
and strabismus

FLOROPRYL®

ISOFLUROPHATE

- highly potent
  — may be effective when other agents fail
- long-acting
  — *in glaucoma*, one instillation a day is often sufficient
  — *in strabismus*, one instillation every two days to one week

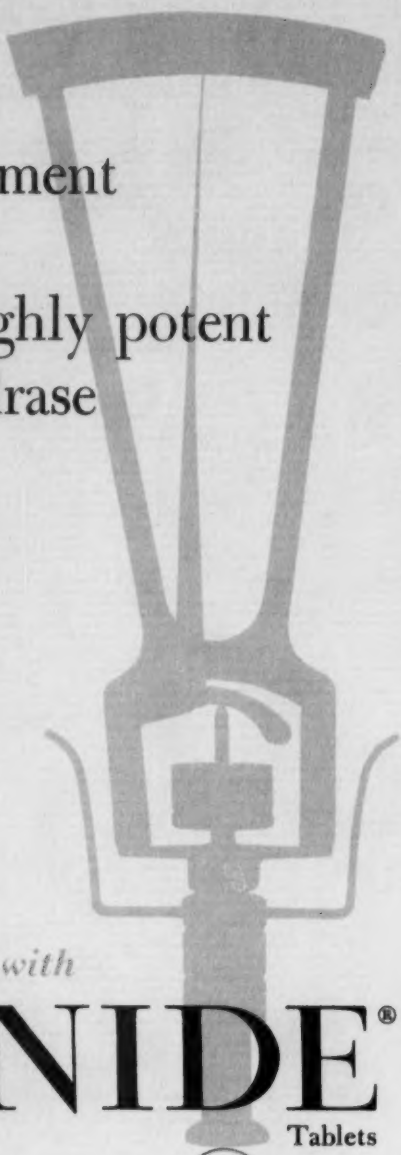
to relieve intraocular pressure in glaucoma	*to enhance peripheral accommodation in strabismus*
aphakic chronic noncongestive congenital and infantile secondary, except in presence of active uveal inflammation preoperative control of intraocular pressure antidote against atropine	nonparalytic, concomitant, convergent (esotropia) *especially:* in the very young when behavior problems preclude glasses to ease the transition from glasses as a temporary substitute for glasses
'Floropryl' is a valuable adjunct to oral 'Daranide' for treatment of certain types of glaucoma	

Dosage: **Either the 0.1 per cent solution or the 0.025 per cent ointment may be used in glaucoma, depending on the strength needed, but only the 0.025 per cent ointment is recommended for strabismus. See package circular or brochure available to physicians on request for detailed information about administration, dosage and precautions.**
Supplied: **for ophthalmic use only – 0.1 per cent solution in peanut oil, in 5 cc. vials. 0.025 per cent ointment, in 3.5 Gm. tubes.**

'FLOROPRYL' and 'DARANIDE' (Dichlorphenamide) are trademarks of Merck & Co., Inc.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

Improved treatment
of glaucoma
with a new, highly potent
carbonic anhydrase
inhibitor

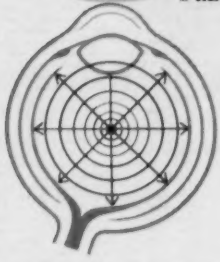


reduce intraocular pressure with

DARANIDE®

DICHLORPHENAMIDE

Tablets



MSD MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

- inhibits aqueous humor formation—lowers intraocular pressure

- reduces danger of metabolic acidosis

- continued effectiveness, even with long-term use

- may be effective when other therapy, including miotics, has failed or has not been tolerated

- smooth control—few side effects

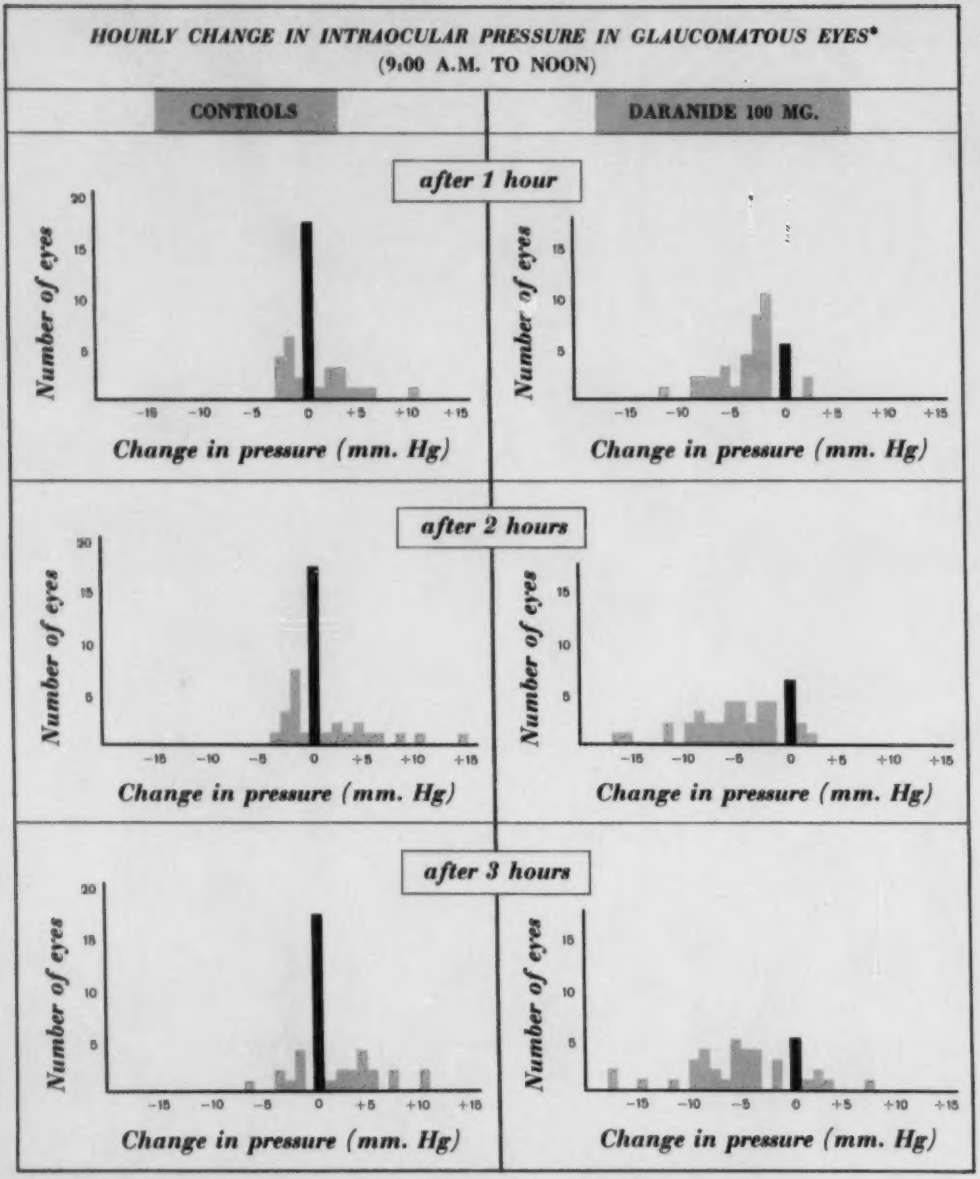
- low dose effectiveness—
  less than with other
  carbonic anhydrase inhibitors
- effective orally—
  unsurpassed absorption after
  oral administration
- fast acting—effective
  within one hour; effect
  maintained six to 12 hours
- economical

for improved treatment of glaucoma

DARANIDE®

DICHLORPHENAMIDE

highly potent 'DARANIDE' reduces intraocular pressure in low dosage


HOURLY CHANGE IN INTRAOCULAR PRESSURE IN GLAUCOMATOUS EYES*
(9:00 A.M. TO NOON)
CONTROLS
DARANIDE 100 MG.
after 1 hour
after 2 hours
after 3 hours
Number of eyes
Change in pressure (mm. Hg)
-15 -10 -5 0 +5 +10 +15
5 10 15 20

*Gonzales-Jiminez, E., and Leopold, I. H.: The Effect of Dichlorphenamide (A Carbonic Anhydrase Inhibitor) on the Intraocular Pressure of Humans, A.M.A. Arch. Ophth. 60:427, Sept. 1958.

'DARANIDE' inhibits aqueous humor formation

EFFECT OF 'DARANIDE' ON AQUEOUS HUMOR DYNAMICS*

	Intraocular pressure mm. Hg		*Facility of outflow mm.³/min./mm. Hg*		*Aqueous flow mm.³/min.*		*Aqueous flow inhibition (%)†*
	Before	*After*	*Before*	*After*	*Before*	*After*	
Normal (30 eyes)	15.8	13.4	0.17	0.17	0.94	0.58	39.5%
Glaucomatous (20 eyes)	30.0	21.9	0.09	0.09	1.36	0.85	39.0%

† $\frac{\textit{Aqueous flow after treatment} - \textit{Aqueous flow before treatment}}{\textit{Aqueous flow before treatment}} \times 100$

**Gonzales-Jiminez, E., and Leopold, I. H.: The Effect of Dichlorphenamide (A Carbonic Anhydrase Inhibitor) on the Intraocular Pressure of Humans, A.M.A. Arch. Ophth. 60:427, Sept. 1958.*

for improved treatment of glaucoma

DARANIDE®

DICHLORPHENAMIDE

Indications

- Chronic simple (wide angle) glaucoma
- Acute congestive (narrow angle) glaucoma
- Chronic congestive glaucoma
- Secondary glaucoma (acute phase)
- Preoperative control of intraocular tension of glaucoma

Dosage

The usual adult dosage range is from 25 to 50 mg. (½ to 1 tablet) once to three or four times daily. Dosage must be carefully adjusted to meet the requirements of the individual patient.

Therapy with 'Daranide' is usually most successful when employed in conjunction with miotics such as pilocarpine, physostigmine, 'Floropryl' (isoflurophate), or 'Carcholin' (carbachol). In acute congestive glaucoma, 'Daranide', with miotics, should be administered promptly in an attempt to bring about rapid reduction of intraocular tension. If this is not quickly relieved, surgery may be mandatory. In chronic congestive glaucoma, surgery may be necessary if the intraocular tension is not brought under control after an adequate trial period of therapy with 'Daranide'.

Precautions

Since 'Daranide' is a carbonic anhydrase inhibitor, certain side effects characteristic of this class of compounds will occur, particularly in the higher dosage ranges. These effects may include anorexia, nausea, vomiting, nervousness, lassitude, depression, confusion, disorientation, sedation, dizziness, ataxia, tremor, tinnitus, paresthesias, and pruritus. Fortunately, the therapeutic amount of 'Daranide' required for most patients is well beneath the level that will produce these effects. When they do occur, reduction of dosage or temporary discontinuance of the drug is indicated.

It is essential to keep a close check on the electrolyte balance of the patient during therapy with 'Daranide', as with patients on any other carbonic anhydrase inhibitor.

Supplied

'Daranide' Tablets, 50 mg., bottles of 100 and 1000.

for improved treatment of glaucoma

DARANIDE®

DICHLORPHENAMIDE

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'Daranide', 'Floropryl' and 'Carcholin' are trade-marks of Merck & Co., Inc.

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Surgical Instruments

NEW Eye Dressing Tray,

McCoy

E-7220 Dressing Tray, Eye, McCOY: compact, containing items needed for post operative treatment.

Designed to hold:

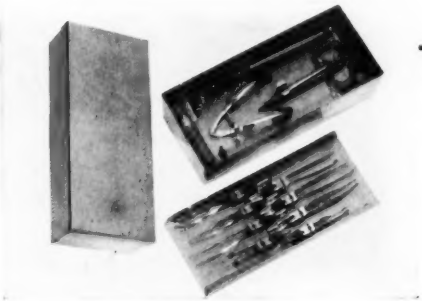
- *1 Each E-7460 Irrigator, DeVilbliss, 1½ oz.*
- *6 Each E-7472 Dropper Bottles, 1 oz. with ground in pipette stopper.*
- *2 Each E-7290 Needle Boxes 3⅛" x 2½"*

Space is provided to hold 6 tubes each of assorted ophthalmic ointments. Ointment not included. There is also space for a supply of eye patches.

Tray only, with fittings, Stainless Steel riveted construction **$39.50**

Tray and fittings, complete with all items listed above, except ointment and eye patches **$57.20**

Sterilizing Box, Iowa Model



E-7225 Sterilizing Box, Iowa Model: one insert has 8 clips to securely hold eye forceps of various sizes. The other insert has a rack for scissors, holders for non-sharp instruments, and space for various small instruments. Rustless **$21.50**

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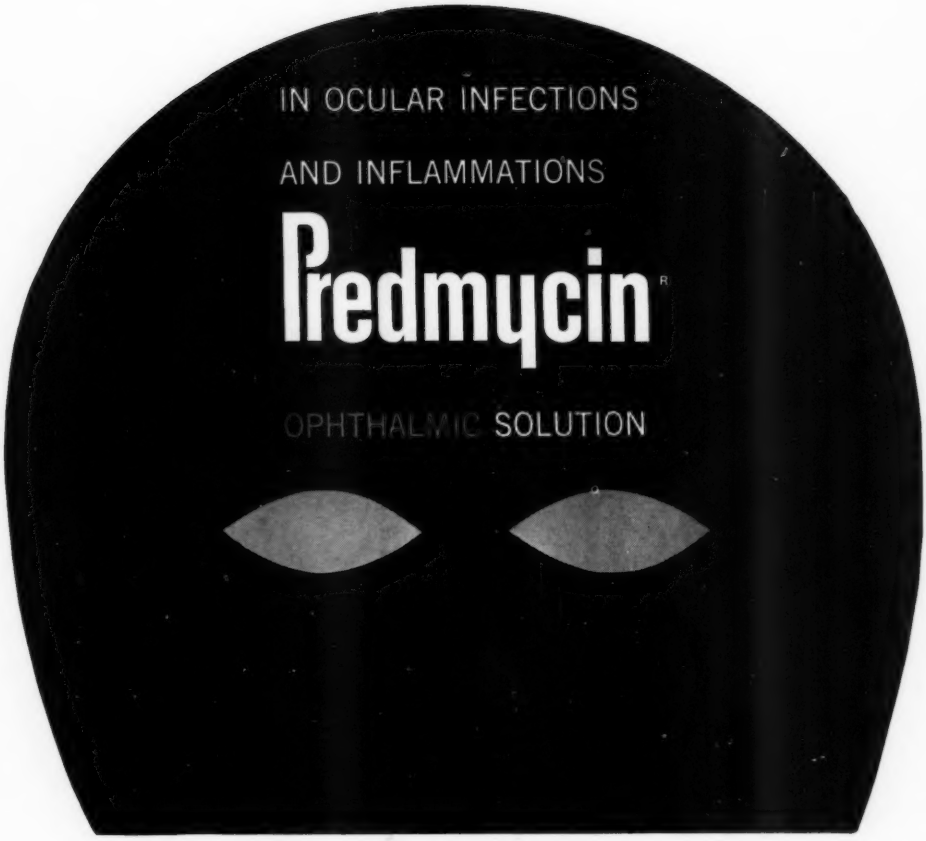

TO TREAT THE PATIENT...THE PATHOGEN...THE INFLAMMATORY PROCESS

New Predmycin Ophthalmic Solution, containing prednisolone, neomycin and a decongestant, provides unsurpassed three-fold therapeutic attack against infectious and inflammatory eye disorders:

- *for the patient: Phenylephrine HCl for rapid improvement of the eye's appearance*
- *for the pathogen:* Neomycin sulfate for its wide antibacterial effectiveness against most pathogens responsible for ocular infections
- *for the inflammatory process:* Prednisolone for its rapid and effective action in checking destructive inflammatory reactions to ocular trauma.

Predmycin combines prednisolone alcohol 0.2%, neomycin sulfate 0.5%, and phenylephrine HCl 0.12%, in a sterile, lubricating solution—for optimal control of infectious, inflammatory and allergic conditions of the eyelids, conjunctiva, cornea, sclera, uveal tract, and following thermal or chemical burns.

DOSAGE: 1 to 2 drops in the eyes two to four times a day.

SUPPLY: In 5 cc. all-plastic dropper bottles—on prescription only.

ALLERGAN CORPORATION *Los Angeles 17, California*